Verdazyl Radicals as Substrates for Organic Synthesis

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
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Abstract

Verdazyl radicals, discovered in 1963, are a family of exceptionally stable radicals defined by their 6-membered ring containing four nitrogen atoms. Verdazyl radicals are highly modular compounds with a large assortment of substitution patterns reported. Their stability and high degree of structural variability has been exploited in the fields of materials, inorganic, polymer and physical chemistry; however their deliberate use as starting materials towards organic synthesis had only been reported in recent years by the Georges lab.

In 2008, the Georges group reported a disproportionation reaction that was observed to occur with 6-oxoverdazyl radicals resulting in azomethine imines capable of undergoing 1,3-dipolar cycloaddition reactions. With this discovery, the door to using verdazyl radicals as substrates towards organic synthesis had been opened. Their utility in synthesis was soon discovered not to be limited to just the cycloadducts their azomethine imine derivatives could generate but also the increasing number of N-heterocycles that could be generated from these cycloadducts via unique rearrangement reactions, a major theme of this thesis. In addition, triphenyl verdazyl radicals, a distinct class of verdazyl radicals, has been shown to react with alkynes by direct radical addition and rearrangement to afford isoquinolines.
As part of this thesis, a new synthetic methodology of generating 6-oxoverdazyl radicals is reported that does not rely on the use of phosgene or hydrazines. This new synthesis allows for the expansion of available alkyl substituents possible on N1 and N5 positions of 6-oxoverdazyl radicals, as well as, generation of unsymmetrical examples of 6-oxoverdazyl radicals with non-identical N1 and N5 alkyl substituents. Employing the new 6-oxoverdazyl radicals synthesized via this method, a study on the effects of different alkyl substituents on the disproportionation reaction of 6-oxoverdazyls was undertaken.

Lastly, given the assortment of N-heterocyclic molecular scaffolds capable of being synthesised starting from verdazyl radicals as precursors, the applicability of verdazyl radicals in making a diversity oriented synthesis (DOS) based library was explored. In a group effort with other Georges lab members, a small library composed of various classes of verdazyl radical derived compounds was synthesized and non-specifically tested for cytotoxicity against acute myeloid leukemia and multiple myeloma cell lines in collaboration with The Princess Margaret Hospital. One example was shown to effectively kill cancer cells in both these lines in 250 μM concentration pointing out the potential of using verdazyl radical based chemistry in drug discovery.
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AML    Acute myeloid leukemia
atm    Atmosphere
Ar     Aryl group
B:     Base
Bn     Benzyl
Boc    tert-Butoxy carbonyl
BPO    Benzoyl peroxide
BST    1-Benzoyloxy-2-phenyl-2-(2’,,6’,,6’-tetramethyl-1’-
piperidinyloxy)ethane
BSV    1-Benzoyloxy-2-phenyl-2-(6-oxoverdazyl)ethane
d     Day(s)
DCM    Dichloromethane
de     Diastereomeric excess
DFT    Density functional theory
DMF    Dimethyl formamide
DMSO   Dimethyl sulfoxide
DOS    Diversity oriented synthesis
EDG    Electron donating group
ee     Enantiomeric excess
ELDOR  Electron-electron double resonance
ENDOR  Electron nuclear double resonance
EPR    Electron paramagnetic resonance
<table>
<thead>
<tr>
<th>Abbreviation</th>
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<td>eq</td>
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</tr>
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<td>ESR</td>
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<td>EtOAc</td>
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<td>EWG</td>
<td>Electron withdrawing group</td>
</tr>
<tr>
<td>FMO</td>
<td>Frontier molecular orbital</td>
</tr>
<tr>
<td>FTIR</td>
<td>Fourier transform infrared spectroscopy</td>
</tr>
<tr>
<td>h</td>
<td>Hour(s)</td>
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<td>High resolution mass spectroscopy</td>
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<tr>
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<td>Highest occupied molecular orbital</td>
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<td>Isopropyl</td>
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<tr>
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<td>Kelvin</td>
</tr>
<tr>
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<td>Living radical polymerization</td>
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<tr>
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<td>Lowest unoccupied molecular orbital</td>
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<td>Molecular orbital</td>
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<td>Multiple myeloma</td>
</tr>
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<td>Melting point</td>
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<tr>
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<td>Nucleophile</td>
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</tr>
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</tr>
<tr>
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<td>Room temperature</td>
</tr>
<tr>
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<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
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<td>SET</td>
<td>Single electron transfer</td>
</tr>
<tr>
<td>SOMO</td>
<td>Singly occupied molecular orbital</td>
</tr>
<tr>
<td>SFRP</td>
<td>Stable free radical polymerization</td>
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<tr>
<td>TEMPO</td>
<td>2,2,6,6-Tetramethyl-1-piperidinyloxy</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Tetramethylsilane</td>
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Chapter 1

1 Introduction

1.1 Stable Radicals

Radicals, a class of subvalent compounds characterized by one or more unpaired electrons, are generally regarded as highly reactive, transient species. The first radical to be detected was the triphenylmethyl radical \( \text{1.2} \) by Gomberg\(^1\) in 1900, generated via the abstraction of a chlorine atom from chlorotriphenylmethane \( \text{1.1} \) by silver metal (Scheme 1-1). Its detection was facilitated by the stabilization afforded by its three phenyl rings making it a persistent radical.

\[
\text{1.1} \quad \text{Cl} \quad \text{Ag} \quad \text{1.2}
\]

*Scheme 1-1.* Formation of the first detected radical.

Non-transient radicals can be loosely described by the terms “persistent”, which Ingold\(^2\) describes as long-lived enough to be studied by spectroscopic methods, and “stable” which are isolable under ambient conditions without appreciable decomposition.\(^3\) These radicals can be stabilized by both steric hindrance provided by bulky groups or through electronic stabilization by electron delocalization. Stable organic radicals, where the unpaired electron is distributed over a number of heteroatoms, are exemplified by nitroxide and verdazyl radicals.
1.2 Verdazyl Radical Overview

Verdazyl radicals are resonance stabilized $7\pi$ cyclic hydrazyl radicals\(^4\) with the general structure shown in Figure 1-1. They are known for their particular stability without having to rely on bulky substituents. Noteworthy is their stability to air and moisture, as well as, their propensity to stay undimerized in both solution and the solid state.\(^5\)

![Figure 1-1. Possible atomic composition and substitution patterns of verdazyl radicals.](image)

Verdazyl radicals were first reported by Trischmann and Kuhn in 1963, discovered serendipitously while alkylating formazans.\(^6\) The initial methylation (reagent not specified by authors) of formazan 1.3 under basic conditions led to a ring closure to form leucoverdazyl 1.4, which in the presence of air oxidized to verdazyl radical radical 1.5 (Scheme 1-2).

![Scheme 1-2. Discovery and first synthesis of a verdazyl radical.](image)

Over the past several decades verdazyl radicals have found applications in the study of molecular magnets,\(^5\) in ESR as a spin labels,\(^7\) as polymerization inhibitors\(^8\) and as mediators in living
radical polymerizations. More recently their usefulness has been demonstrated in generating heterocyclic small molecules, which will be discussed in detail later in the thesis.

Verdazyl radicals can be readily categorized into two main groups. The first has a sp$^3$ hybridized carbon at the 6-position exemplified by 1.5 in Scheme 1-2. The other group is comprised of the 6-oxoverdazyl radicals, first reported by Neugebauer in 1980. They have a sp$^2$ hybridized carbon at the 6 position in the form of a carbonyl or thiocarbonyl group. Other verdazyl radical types that have been reported include those with phosphorus moieties or a boron atom.

The exceptional stability of verdazyl radicals is attributed to the delocalization of its unpaired electron across all four nitrogen atoms in the ring with the odd electron residing in a low energy $\pi^*$ SOMO, as indicated by DFT calculations. The SOMO orbital picture is shown in Figure 1-2 with a nodal plane passing through C3 and C6.

![Figure 1-2. SOMO orbitals of a verdazyl radical with phases shown.](image)

Experimental evidence from electron-electron double resonance (ELDOR), electron nuclear double resonance (ENDOR), dynamic nuclear polarization (DNP) and NMR spectroscopy supports this theory. A nodal plane in the SOMO passes through C3 so no direct spin delocalization is observed on substituents at that position, only very small spin polarization effects. When the substituents at N1 and N5 are aromatic, as in Figure 1-2, a trace amount of
spin delocalization can be observed in the aromatic systems; however the major spin bearers are the nitrogen atoms, accounting for 80-85% of the spin density.

Regarding the structure of the verdazyl radical ring, X-ray diffraction studies of triphenyl verdazyl radical, representing the verdazyl radicals with an sp\(^3\) center at C6, show a deviation from planarity as defined by the four nitrogen backbone in the ring.\(^{16}\) The C6 center, the methylene, is bent out of the plane resulting in a half-boat conformation. In contrast, the 6-oxoverdazyl radicals, representing the verdazyl radicals with an sp\(^2\) center at C6, adopt a planar conformation of the 6-membered ring.\(^{17}\)

1.3 Verdazyl Radical Synthesis

Kuhn and Trischmann’s original verdazyl radical paper\(^6\) in 1963 is the basis for one of the most common syntheses of triaryl verdazyl radicals with sp\(^3\) centers at the C6 position. The synthesis, shown in Scheme 1-2, begins with a methylation, or an alkylation with any other primary alkylating agent, of formazan followed by an oxidation to give the verdazyl radical.\(^6,18\) The main drawback using this method in making triaryl verdazyl radicals is the low tolerance for electron withdrawing groups on the C3 aryl group.\(^{18}\)

More recently, Katritsky et al. reported a synthesis starting with formazan and an aldehyde in acidic conditions to form a 6\(\pi\) verdazylium cation ring.\(^{19}\) This verdazylium ion 1.6 is reduced with ascorbic acid in base to an anion that is subsequently oxidized in air to the verdazyl radical (Scheme 1-3).
Scheme 1-3. Katritsky’s synthesis of triphenyl verdazyl radical using formaldehyde.

This synthesis shows more versatility for groups on the C3 aryl group and can be used with substituted aldehydes to introduce substituents at the C6 position. The synthesis can also be performed without acid if the starting formazan is not electron poor.\textsuperscript{20} The formaldehyde based synthesis can be applied to the Mannich reaction opening up an avenue to introduce amine substituents at the C6 position.\textsuperscript{19} Scheme 1-4 shows an example of this Mannich modification using diamine 1.7 to form the di-verdazyl radical 1.8. Synthesizing diverdazyl radicals can also be accomplished by using di-formaldehydes or dialkylation agents to form a linker between the C6 positions.

Scheme 1-4. Mannich modification of the Katritsky synthesis.
A synthesis for 6-oxoverdazyl radicals was first reported in 1980 by Neugebauer and Fischer.\textsuperscript{11} Reacting alkyl hydrazides 1.10 with phosgene 1.9 gives bis-alkylhydrazides of carbonic acid, 1.11, that condense with aldehydes to afford tetrazinanones 1.12. The tetrazinanones can then be oxidized to the verdazyl radicals 1.13 (Scheme 1-5).

\[ \text{Scheme 1-5. 6-Oxoverdazyl radical synthesis.} \]

Verdazyl radicals with a thiocarbonyl group at the C6 position can be made by substituting phosgene with thiophosgene.\textsuperscript{21} Four equivalents of hydrazine are used as two are sacrificed to neutralize the hydrochloric acid formed during the course of the reaction. Substitution of R’ is highly variable due to the commercial abundance of aldehydes. The disadvantage of this synthetic approach is in the first step. With the hydrazine attacking the phosgene, the N-substituent cannot be too bulky otherwise the N’ will act as the nucleophile instead and result in the wrong product, 1.14, being formed (Scheme 1-6).

\[ \text{Scheme 1-6. Possible attacks of isopropyl hydrazine on phosgene.} \]
Another problem is the limited commercial availability of different alkyl hydrazines as reflected by only methyl and benzyl examples being reported in literature. In addition, phosgene gas is not trivial to handle and is highly toxic. This issue was addressed by using triphosgene, a solid, as a substitute.\textsuperscript{22} However, once made, tetrazinanones oxidize fairly easily to verdazyl radicals with a variety of oxidants such as K\textsubscript{3}Fe(CN)\textsubscript{6}, PbO\textsubscript{2}, Ag\textsubscript{2}O and NaIO\textsubscript{4}.

In order to get around the issue of incompatibility of phosgene with sterically bulky hydrazines, Brook et al. developed a synthesis involving a Boc-protected hydrazine.\textsuperscript{23} This method was applied to the synthesis of 1,5-diisopropyl verdazyl radicals (Scheme 1.7).

Using t-butylcarbazate 1.15 as the hydrazine source allows for the introduction of the desired alkyl group via a condensation of a ketone or aldehyde to form 1.16 that is subsequently reduced to give 1.17. The alkylated t-butylcarbazate 1.17 subsequently reacts with phosgene, without ambiguity as to which nitrogen will act as the nucleophile, forming 1.18 exclusively. Following this, the Boc protected groups are cleaved with acid giving bis-dialkyl hydrazides 1.19 that can...
be condensed with an aldehyde to form a tetrazinanone 1.20 that can then be oxidized to verdazyl radical 1.21. The Milcent group developed a synthesis for 6-oxoverdazyl radicals that allows for differing substituents on the N1 and N5 positions. This method entails the condensation of an aryl hydrazine 1.22 with an aldehyde to form a hydrazone 1.23 that is then reacted with phosgene to afford a carbamoyl chloride, 1.24. The reaction of 1.24 with another aryl hydrazine, followed by ring closure and oxidation provides the verdazyl radical product (Scheme 1-8).

Scheme 1-8. Milcent’s verdazyl radical synthesis.

The Brook group capitalized on this synthesis combining it with their t-butylcarbazate approach to form the unsymmetrical 1-isopropyl-3,5-di-(2-pyridyl)-6-oxoverdazyl radical in their studies of verdazyl radical metal complexes. A synthesis enabling the synthesis of unsymmetrical verdazyl radicals with 1,5-dialkyl substitutions without the use of phosgenes or hydrazines was recently developed and is the subject of chapter 8.
Phosphaverdazyl radicals are made with a phosphorus center at either the 3 or 6 positions. The heterocyclic chemistry for their syntheses was first introduced in 1976 by Navech\textsuperscript{27} with the synthesis of the phosphorus containing precursor heterocycles of this class of verdazyl radicals and greatly elaborated on by Hicks et al.\textsuperscript{28} To prepare phosphaverdazyl radicals with the phosphorus at the 6 position, Hicks et al. used a modified Markovskii\textsuperscript{12a} procedure using the orthoester, trimethyl orthobenzoate \textsuperscript{1.29}, to close the ring with the bis-methylhydrazide of phenylphosphonic acid \textsuperscript{1.28} to form the corresponding leucoverdazyl \textsuperscript{1.30}. In this case the leucoverdazyls are relatively stable necessitating an oxidation step to obtain the final radical product (Scheme 1-9).

![Scheme 1-9. Synthesis of a 6-phosphaverdazyl radical.](image)

The synthesis of the 3-phosphaverdazyl radical \textsuperscript{1.32} starts with \textit{bis}-methylhydrazide, used in 6-oxoverdazyl radical syntheses, but in this case condensed with trichlorodiphenylphosphorane in lieu of an aldehyde. Again, the leucoverdazyl \textsuperscript{1.31} formed is stable to air and needs to be oxidized, in this case with I\textsubscript{2} (Scheme 1-10).
The last class of verdazyl radicals to be discussed are boron containing verdazyl radicals that are actually radical anion species and first reported in 2007 by Hicks et al.\textsuperscript{29} This synthesis follows analogously to the synthesis of triphenylverdazyl radicals discussed at the beginning of this section starting with a formazan reacting with boron triacetate and followed by reduction with cobaltocene (Scheme 1-11).

\textbf{Scheme 1-11.} Synthesis of a borataverdazyl radical.

### 1.4 Historical Verdazyl Radical Chemistry

Although verdazyl radicals have been known since 1963, few reactions involving them have been reported. Verdazyl radicals are susceptible to radical coupling reactions with alkyl radicals\textsuperscript{30} and are prone to self-decomposition, perhaps the most noteworthy reaction of this is the thermal decomposition of triphenylverdazyl radical reported by Neugebauer\textsuperscript{31} resulting in a 1,2,4-triazole which decomposed further at higher temperatures to lose aniline as shown in Scheme 1-12.
Scheme 1-12. Thermal decomposition of triphenyl verdazyl radical.

In 1988, Neugebauer\textsuperscript{21} reported a 6-oxoverdazyl radical self-coupling reaction that occurred over 48 hours in the presence of formic acid (Scheme 1-13). The coupling product was produced in 8\% yield and a mechanism for its formation was not provided.

Scheme 1-13. Verdazyl radical “dimerization” reaction.

In section 5.2 of this thesis a disporportionation of 1,5-dimethyl-3-phenyl-6-oxoverdazyl radical will be discussed that offers a possible explanation for this coupling product.
1.5 Application of Verdazyl Radicals

The unique properties of verdazyl radicals have made them ideal subjects in several fields of study. Traditionally, verdazyl radicals have been used in the study of molecular magnets,\(^5\) in ESR as a spin labels,\(^7\) as polymerization inhibitors\(^8\) and as mediators in living radical polymerizations.\(^9\)

Conventional magnetic materials are comprised of spin active metals or metal oxides whose unpaired electrons contribute to the overall magnetic moment of the material. Molecular magnets are distinct in that their building blocks are molecular, often organic in nature. The stability of verdazyl radicals under ambient conditions has pushed them to the forefront of this field of research. Several approaches are used in these studies including linking verdazyl radicals together by covalent bonds to form di- and tri-radical systems. Another popular approach is making hybrid organometallic systems where a spin active metal is complexed with verdazyl radicals. The modular nature of verdazyl radicals allows for incorporation of complexation favouring groups such as pyridyls.\(^5\) Because of these properties, verdazyl radicals have also proven useful as spin labels in biological systems. By coupling a stable radical to a target biomolecule, such as an enzyme, ESR can be used to study its environment.\(^32\)

Radical driven polymerizations are one of the major ways in which industrially relevant materials are made. Stable radicals have been useful in studying the kinetics of these systems by acting as polymerization inhibitors.\(^8\) Because they will only couple with the growing polymer chain and not each other, they are useful in determining initial rates of polymerization, as well as concentrations of propagating species.\(^33\)

Stable radicals have found use in the field of living radical polymerizations as mediators. In this case, stable radicals are not used as initiators but as capping agents, coupling to the propagating
radical chain, in effect pausing the polymerization. Georges et al. successfully demonstrated the use of verdazyl radicals to this type of polymerization in styrene and $n$-butyl acrylate. Living radical polymerization has allowed a degree of control in radical polymerization allowing for low polydispersity indexes (PDI’s), as well as creating block co-polymers.

1.6 Summary

Verdazyl radicals, along with TEMPO and a few other stable radicals, form an elite class of radicals known as stable radicals which can be isolated and stored for long periods of time at ambient temperatures without appreciable decomposition. Since they were first reported in 1963, verdazyl radicals have found uses as building blocks of molecular magnets, ESR spin labels, polymerization inhibitors, mediators in living radical polymerizations and very recently as substrates in the synthesis of heterocyclic small molecules. Several syntheses of verdazyl radicals were developed, bringing about their rich structural diversity as shown in Figure 1-1. Despite their rich structural diversity and multiple heteroatoms, chemistry using verdazyl radicals as reagents has remained largely unexplored and holds a lot of potential which will be illustrated in subsequent chapters.

1.7 References


Chapter 2

2 1,3-Dipolar Cycloadditions

2.1 Introduction to Cycloadditions

Cycloadditions constitute a subset of reactions known as pericyclic reactions. Unlike reactions in organic chemistry that involve a nucleophile and electrophile pair, pericyclic reactions are largely governed by orbital interactions rather than electrostatics. Cycloadditions are an invaluable method of making carbon-carbon bonds to form ring systems.\(^1\) The most famous example of a cycloaddition reaction is the Diels-Alder reaction depicted in its simplest form in Scheme 2-1. The Diels Alder is an example of a \([4+2]\) cycloaddition because of the number of \(\pi\) electrons in each component.

![Scheme 2-1. Simplified Diels-Alder cycloaddition.](image)

In this reaction, \(\sigma\) bonds are created at the expense of \(\pi\) bonds via a concerted mechanism. Frontier molecular orbital theory (FMO) is often used to explain and predict cycloaddition reactions. FMO theory is a simplification of MO theory described by Fukui to take into account only the most important interactions: highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) interactions.\(^2\) According to the basics of FMO, the orbital phases between the reactants’ respective HOMOs and LUMOs must align in a symmetry allowed fashion. Which HOMOs and LUMOs are used is dictated by their relative energies, the
smaller energy gap between the two pair combinations being favoured. Regioselectivity is predictable based on largest orbital coefficients of each reactant interacting first, setting up the reactants relative positions. FMO theory predicts the results of pericyclic reactions quite accurately, however it does not take into account factors such as secondary orbital interactions or sterics.\textsuperscript{3}

The Woodward Hoffman rules defined by Woodward and Hoffman in 1965 provides a complementary method to predicting the outcome of pericyclic reactions describing them as allowed or forbidden based on electron counting.\textsuperscript{4} The rule states that for thermal pericyclic reactions to be allowed, the total number of \((4q+2)_s\) and \((4r)_a\) components must be odd where \(q\) and \(r\) are integers, the subscript “s” indicates a suprafacial addition and subscript “a” indicates antarafacial addition of the reactants.\textsuperscript{5}

## 2.2 1,3-Dipolar Cycloadditions

1,3-Dipolar cycloadditions have become a very useful way of making 5-membered heterocycles, popularized and greatly developed by Huisgen\textsuperscript{6} although examples of 1,3-dipolar cycloadditions date back to 1888 in the literature.\textsuperscript{7} Whereas in the Diels Alder reaction, reactants are referred to as dienes, \textsuperscript{2.1} and dieneophiles, \textsuperscript{2.2}, in 1,3-dipolar cycloadditions their respective counterparts are called dipoles, \textsuperscript{2.3}, and dipolarophiles, \textsuperscript{2.4} (Scheme 2.2). 1,3-Dipolar cycloadditions are also \([4+2]\) cycloadditions (based on electron count) with the dipole being isoelectronic to an allyl anion with \(4\pi\) electrons. The 1,3-dipolar cycloaddition is often called a \([3+2]\) cycloaddition based on atom count but this is discouraged since electron counts are a more systematic classification.\textsuperscript{5} The dipole component of this reaction is highly variable and usually heteroatomic, common examples are shown in Figure 2-1. Most often, 1,3-dipoles are drawn in their ylide forms as seen in Figure 2-1 since all atoms in this form have a complete octet.
Figure 2-1. Examples of 1,3-dipoles (shown in their ylid form)

Most 1,3-dipoles can be classified as being of the allyl type or the propargyl type, in both cases they are resonance stabilized. The general scheme by which 1,3-dipolar cycloadditions occur is illustrated in Scheme 2-2.

Scheme 2-2. General 1,3-dipolar cycloaddition scheme.

The "concertedness" of 1,3-dipolar cycloadditions has been, in the past, a matter of debate, most notably between Huisgen and Firestone. Huisgen argued a concerted mechanism while Firestone favoured a stepwise diradical mechanism.
The debate was concluded in favour of the concerted mechanism based on the observation that these cycloadditions always proceed with retention of configuration\textsuperscript{10}. Further support for the concerted mechanism was provided by DFT calculation reported by Houk et al.\textsuperscript{11} The diradical mechanism notion has not been completely dismissed however. 1,3-Dipoles do contain a measure of diradical character especially those of the carbonyl family displaying up to 1/3 diradical character.\textsuperscript{10} Furthermore, reactions where the dipole and dipolarophile are highly substituted can stabilize radical intermediates and can mechanistically often be interpreted with either mechanism.

1,3-Dipolar cycloadditions are accurately explained using FMO theory. The dipole is $4\pi$ electron component with three energy levels and is depicted in Figure 2-2. The HOMO of the dipole has a node on the central atom and two anti-bonding interactions in its LUMO.

**Scheme 2-3.** Firestone’s diradical mechanism.

**Figure 2-2.** FMO diagram of potential dipole-dipolarophile interactions.
Depending on the heteroatoms in the dipole and substituents involved, the energies of the orbitals and their coefficients can vary. For the 1,3-dipolar cycloaddition to proceed, the orbitals of the dipole and dipolarophile need to be aligned such that the ends of each component are in phase and interact constructively. This is the case when either the HOMO of the dipole interacts with the LUMO of the dipolarophile or vice versa as seen in figure 2-3.

![Alignment of FMO’s for 1,3-DC.](image)

**Figure 2-3.** Alignment of FMO’s for 1,3-DC.

Which interaction occurs during the cycloaddition depends on the HOMO/LUMO energy gap between the components. As depicted in Figure 2-2, the energy gap between the HOMO of the dipole and LUMO of the dipolarophile is lower and proceeds thusly.

Sustmann classified three different cases of dipole-dipolarophile interactions based on relative HOMO/LUMO energy gaps. Sustmann I represents the case shown in Figure 2-2 where the dipole HOMO to dipolarophile LUMO energy gap is smaller than HOMO dipolarophile to LUMO dipole gap and the cycloaddition would proceed via the interaction illustrated in Figure 2-3a. Sustmann III is the opposite case and is represented by Figure 2-3b. Sustmann III occurs when the dipole has electron withdrawing groups present resulting in the lowering of its LUMO energy and the dipolarophile has donating groups, raising its HOMO energy level. Sustmann II is an intermediate case where the HOMO to LUMO gaps between reactants are comparable and there is no clear lower energy pathway between HOMO/LUMO pairs. In such cases activation
energies are usually high and Lewis acids or other additives can be used to perturb the energy level of one or both reactants to decrease the activation barrier.\textsuperscript{13}

In real-world systems, cycloaddition components are often not symmetrical, which affects their orbital coefficient distribution. As mentioned previously, the orbitals with the largest coefficients on each component will interact earliest and dictate the regioselectivity of the cycloaddition. This phenomenon is illustrated in Scheme 2-4 with a specific example, 4-nitrophenyl azide reacting with 2,3-dihydrofuran.\textsuperscript{14}

\textbf{Scheme 2-4.} FMO diagram of regioselectivity with orbital coefficients.

2.3 Catalysis in 1,3-Dipolar Cycloadditions

Perhaps the most famous recent example of 1,3-dipolar cycloaddition catalysis has been that of the azide-alkyne Huisgen cycloaddition reaction catalyzed by Cu(I). In 2002, two groups, Sharpless et al.\textsuperscript{15} and Mendal et al.\textsuperscript{16} independently reported the copper catalyzed cycloaddition
of azides with alkynes. This type of catalysis not only allowed for high yields but also afforded near complete regioselectivity and milder reaction conditions for generating 1,2,3-triazoles. Copper acts by forming a cuprous acetylide with a terminal alkyne which via a stepwise, rather than concerted process, cycloadds to an azide regioselectively to yield a 1,4-disubstituted 1,2,3-triazole. Although Cu(I) is the active catalyst, it has been found that introducing Cu(II) with a reducing agent and forming Cu(I) \textit{in situ} works better since Cu(I) is not very stable, particularly in aqueous solutions. A typical reaction is shown in Scheme 2-5. This reaction has become a popular way of generating tetrazoles by using nitriles in place of alkynes.\textsuperscript{17} This chemistry has been hailed as a prime example of “click chemistry”, a concept outlined by Sharpless\textsuperscript{18} and has actually become synonymous with that term.

![Scheme 2-5. Typical conditions for Cu(I) catalyzed azide/alkyne cycloaddition.](image)

An analogous Ag(I) version of this transformation has recently been reported\textsuperscript{19}, as well as a ruthenium based example. The ruthenium catalysis is shown to work equally well with internal, as well as external alkynes, suggesting a distinct mechanism and alternatively yields triazoles with the opposite 1,5 regioselectivity.\textsuperscript{20}

Lewis acids have been used extensively to catalyze the Diels-Alder reaction by activating the dienophile.\textsuperscript{5} Not only does Lewis acid catalysis improve reaction times and yields but also improves regioselectivity and stereoselectivity. The same principles that would activate a dienophile also works to activate dipolarophiles in Sustmann I type 1,3-dipolar cycloadditions.
When a dipolarophile, such as an $\alpha,\beta$-unsaturated carbonyl, for example acrolein, is complexed with a Lewis acid like AlCl$_3$, electron density is withdrawn which lowers the dipolarophiles’ LUMO and hence, lowers the energy gap between it and the HOMO of the dipole. Additionally, the LUMO becomes even more polarized making the LUMO orbital coefficient on the $\beta$-carbon even larger and that of the $\alpha$-carbon even smaller, resulting in greater selectivity.$^{21}$ This effect is shown in figure 2-4.

![Figure 2-4. A Lewis acid’s effect on acrolein’s LUMO.](image)

Chiral Lewis acids can also be employed to drive enantioselective cycloadditions, examples of which will be discussed in the next section.

### 2.4 Azomethine Imines in 1.3-Dipolar Cycloadditions

Azomethine imines, shown in Figure 2-1, usually generated *in situ*, belong to the allyl-type family of dipoles and are typically highly reactive.$^{22}$ Azomethine imines were first reported in 1893 by Schad,$^{23}$ however they were not demonstrated to act as dipoles in 1,3-dipolar cycloaddition reactions until 1917.$^{24}$ Their composition makes them ideal for use in generating pyrazolo compounds 2.5 when reacted with alkenes and alkynes (Scheme 2-6).
Azomethine imines were brought out of obscurity by Huisgen in a 1963 review of 1,3-dipolar cycloadditions. They need not be limited to linear examples and form interesting fused systems upon cycloaddition when incorporated in a ring (Scheme 2.7).

**Scheme 2-6.** General 1,3-DC with azomethine imines.

**Scheme 2-7.** (3,4-Dihydroisoquinolinium-2-yl)(4-nitrophenyl)amide 1,3-DC.
In this example, Huisgen reacted a series of N-arylamino-3,4-dihydroisoquinolinium salts, \( \text{2.6} \), with pyridine to form the respective azomethine imine \( \text{2.7} \) which cycloadded with norbornene in near quantitative yield to give product \( \text{2.8} \).\(^{25}\) Interestingly, in the absence of a dipolarophile, product \( \text{2.9} \), the result of a “head to tail” dimerization, is observed to form reversibly.

This “head to tail” dimerization is very interesting in the context of verdazyl radical chemistry since an identical form of dimerization was observed by Neugebauer in 1988 to occur with verdazyl radicals\(^{26}\) seen in \( \text{1.33} \) (Scheme 1-13). This would suggest verdazyl radicals somehow form azomethine imines. However, verdazyl radicals were not used as precursors to azomethine imines towards heterocycle synthesis until 2008.\(^{27}\)

Azomethine imines need not be stand alone reagents. Chemists often need to employ creativity to synthesize their desired compounds and take advantage of an opportunity when it arises; an azomethine imine can be built into a molecule followed by an intramolecular cycloaddition to form a necessary ring architecture. Scheme 2-8 shows an example by Oppolzer where this is accomplished for the synthesis of tetrahydrochromenopyrazole.\(^{28}\)

![Scheme 2-8. Intramolecular 1,3-dipolar cycloaddition with an azomethine imine.](image-url)
Sydnones, **2.10**, a family of cyclic azomethine imines similar to the more common münchnones (cyclic azomethine ylides), form pyrazoles upon loss of CO\(_2\) when reacted with alkynes. Harrity et al. demonstrated their importance in generating pyrazole boronic esters **2.12** via 1,3-dipolar cycloaddition reactions.\(^{29}\) Scheme 2-9 illustrates this with the cycloadduct intermediate **2.11** shown before it loses CO\(_2\) in order to aromatize.

![Scheme 2-9. Synthesis of pyrazole boronic acids by Harrity et al.\(^{29}\)](image)

Sydnone imines have also been shown to act as dipoles in 1,3-DC except with the elimination of an isocyanate instead of carbon dioxide.\(^{30}\)

Enantioselective catalysis has become an important area of research in chemistry that has extended into 1,3-dipolar cycloadditions. The first such report was by Inomata et al. in 1993 with nitrile oxides and allyl alcohols giving ee’s as high as 96% in the resultant 2-isoxazolines.\(^{31}\) Jorgensen et al. in 1994 showed enantioselective 1,3-dipolar cycloaddition reactions using nitrones with the use of Ti(IV) complexes to act as Lewis acids to activate the alkenes to give up to 62% ee.\(^{32}\) It wasn’t, however, until 2002 that azomethine imines were used in a catalytic enantioselective synthesis. Kobayashi et al.\(^{33}\) used Zr(OPr)\(_4\) with a BINOL ligand to catalyze an intramolecular azomethine imine 1,3-DC reaction (Scheme 2-10).
The unconjugated electron rich alkenes suggest this is a case of a Sustmann III type 1,3-dipolar cycloaddition reaction. The Zr Lewis acid catalyst, unlike previously described, complexes with the dipole instead, lowering its LUMO and allowing better access for the alkene’s HOMO to react. Kobayashi notes that these cycloadducts can be used in the making of chiral diamine ligands by the reductive N-N bond cleavage using SmI₂.

Fu et al. described a case where a Cu(I) catalyzed azide/alkyne cycloaddition reaction was performed enantioselectively using phosphaferrocene-oxazoline ligands. This reaction, as with standard Cu(I) azide/alkyne cycloaddition reactions, was presumed to go through a copper acetylide intermediate, only this time the copper was carrying with it chiral ligands. In this case, alkynes with electron withdrawing groups or conjugating groups gave the best results with near quantitative yields and 96% ee.

The first example of an azomethine imine 1,3-dipolar cycloaddition used in a total synthesis was demonstrated by Jacobi et al. in making a pyrolidine ring, an intermediate step towards the final product saxitoxin (Scheme 2-11).
Scheme 2-11. Azomethine imine 1,3-DC step of saxitoxin synthesis.

Construction of complex polycyclic ring systems containing multiple nitrogen atoms is neatly accomplished with azomethine imines and a 1,3-dipolar cycloaddition reaction.

Another such example is the total synthesis of nankakurine A and B by Overman et al.\textsuperscript{36} The key step involving an azomethine imine 1,3-dipolar cycloaddition reaction is shown in Scheme 2-12. The azomethine imine 2.13 is generated by a condensation with a hydrazide group and methyl chloroformate under basic conditions. A 1,3-dipolar cycloaddition reaction with an alkene on an adjacent ring gives product 2.14 in an impressive 82% yield.

Scheme 2-12. Key 1,3-DC reaction step in the synthesis of nankakurine A and B.
Once this key ring system was constructed four further steps yielded the final natural product. Other alkaloids, including those of the lucidine family, contain such ring systems and could also conceivably be synthesized via azomethine imines.

2.5 Summary

Cycloaddition reactions are one of the major ways organic chemists are able to create carbon-carbon bonds and are invaluable particularly in generating ring systems. The reactivity of this class of reactions, including regio- and stereoselectivity, is predictable based on FMO theory and the Woodward-Hoffman rules. 1,3-Dipolar cycloaddition reactions are especially useful for generating 5-membered heterocycles with a wide array of dipoles. Azomethine imines, discussed at length, are great precursors to nitrogen containing heterocycles and have been used in total syntheses of natural products, especially alkaloids. Catalysis of 1,3-dipolar cycloadditions is an active area of research which can greatly improve yields, generate chiral centers and direct regioselectivity. Structurally novel azomethine imines will be discussed in chapter 6 on how they are derived from verdazyl radicals and lead to several classes of interesting N-heterocycles.

2.6 References


15. Rostovtsev, V.V.; Green, L.G.; Fokin, V.V.; Sharpless, B.K. Angew. Chem. 2002, 114, 14, 2708-2711.


3 Five-Membered N-Heterocyclic Rearrangements

3.1 Introduction
Heterocycles are ubiquitous in organic chemistry and are common targets for synthesis. The presence of heteroatoms in a ring adds an extra dimension to its reactivity and properties such as nucleophilicity, stabilization of conformations via anomeric effect and electronegativity. Nitrogen is a particularly interesting heteroatom to appear in a ring because of its ease of inversion. Instead of creating a permanent chiral center, a nitrogen atom with three different substituents along with its lone pair rapidly inverts resulting in conformational changes. Rings or fused ring systems with multiple nitrogens can undergo multiple changes in conformation sometimes giving way to rearrangements. These heterocyclic rearrangements proceeding by temporary ring opening followed by closure are of great interest to chemists both synthetically and mechanistically because they lead to new classes of compounds that are otherwise difficult to access by other procedures.

3.2 Dimroth Rearrangements
The Dimroth rearrangement is one of the most well known five-membered N-heterocyclic rearrangements. Its discovery and mechanism were described by Dimroth\(^1\) in 1909. The Dimroth rearrangement can be most simply described as a switching of places between an exocyclic nitrogen and an endocyclic nitrogen via a ring opening and subsequent closure. Scheme 3-1 illustrates the mechanism with a simple example.\(^2\)
**Scheme 3-1.** Dimroth rearrangement mechanism.

Upon ring opening of triazole 3.1, intermediate 3.2 has a single bond allowing free rotation. In this step the endo and exocyclic nitrogens switch places 3.3 and the ring closes back to form triazole 3.4 with exchanged nitrogens. By using a $^{15}$N label on the exocyclic nitrogen, Brown et al.\(^3\) in 1961 confirmed this mechanism by showing the $^{15}$N as endocyclic in the rearrangement product.

Dimroth rearrangements need not be limited to monocyclic examples. Nucleic acids upon methylation, when exposed to base, undergo a Dimroth rearrangement. Studies on the mechanism by Engel\(^4\) show this is the case in Scheme 3-2.

**Scheme 3-2.** Adenosine Dimroth rearrangement as elucidated by Engel.\(^4\)
Methylation occurs almost exclusively on the N1 position of **3.5** of adenosine. The subsequent rearrangement is seen to proceed via a hydrolysis reaction which opens the ring to give **3.6** allowing the endo and exocyclic nitrogens to exchange. Once ring closure occurs through condensation, the final adenosine **3.7**, with the translocated N-methyl, is formed.

A more recent example by Etman\(^5\) shows a Dimroth rearrangement occurring in a fused ring system where a nitrogen atom is exchanged between two rings. This example still follows the same basic mechanism with the subtlety being the exchanging nitrogen is part of another ring (Scheme 3-3).

![Scheme 3-3. Dimroth rearrangement within a fused ring system.](image)

In this case, the Dimroth rearrangement is being driven by a nucleophilic attack. These types of rearrangements occur faster with electron withdrawing groups present since the incoming negative charge can be stabilized by delocalization. Rearrangements with highly conjugated intermediates are also observed to be more favourable.\(^6\)

Dimroth rearrangements can also occur in some cases without the assistance of a base/acid or nucleophile. A recent paper by Subbonita et al.\(^7\) shows a case where heat alone drives a Dimroth rearrangement (Scheme 3-4).
closes by attack of the amide nitrogen on the ketene to form the rearrangement product. The energy of activation for the ketene formation is 24-34 kcal/mol, which means that at the given reaction temperature this occurs spontaneously.

A Dimroth rearrangement was used by Itaya et al. to synthesize the purine aplidiamine-9-β-D-ribofuranoside, a metabolite isolated from marine ascidia. The key step is shown in Scheme 3-5.
Bakulev et al.\textsuperscript{9} developed a novel approach to tricyclic 1,3,6-thiadiazepines involving a Dimroth rearrangement. In this synthesis, however, an endocyclic sulfur atom switches places with an exocyclic nitrogen atom (Scheme 3-6). The reaction sequence is one-pot, starting with a 1,2,3-thiadiazole undergoing a Smiles rearrangement, essentially an intramolecular nucleophilic aromatic substitution followed by a Dimroth rearrangement. A second nucleophilic aromatic substitution results in cyclization and loss of –SH to form the thia diazepine.

\textbf{Scheme 3-6}. Bakulev synthesis of 1,3,6-thiadiazepines.\textsuperscript{9}
3.3 Other Rearrangements

Although the Dimroth rearrangement is a famous example of a five-membered N-heterocyclic rearrangement there are several lesser known recent examples worth mentioning. These following examples are a few interesting highlights to show some mechanistic details of recently documented rearrangements.

Ariga et al.\textsuperscript{10} reported a transformation where upon treatment with enolates of $\beta$-keto esters and $\beta$-diketones, 2-methyl-4-nitroisoxazolin-5-one rearranged to give 3-nitropyroles. The example in Scheme 3-7 shows 4-nitroisoxazolin-5-one 3.11 being nucleophilically attacked by sodium 1-ethoxy-1,3-dioxobutan-2-ide, 3.12, causing decarboxylation to occur to afford an opened ring intermediate 3.13 which subsequently closes to form the pyrrole 3.14.

![Scheme 3-7. Ariga et al.\textsuperscript{10} rearrangement of isoxazolinones to pyrroles.](image)

This mechanism is unusual not only in that a nitrogen atom is attacked by a nucleophilic anion but also there is a Michael-acceptor site already in 3.11 that is the much more obvious electrophilic center. Nonetheless, the authors managed to isolate protonated 3.13 by quenching the reaction mixture with NH$_4$Cl, affirming this to be the most likely mechanism. This example highlights the subtle nature of the reactivity of heterocycles.
A transformation involving 1,2,5-thiadiazole rearranging to an imidazole via a desulfurization reaction was reported by Butler et al.\textsuperscript{11} When thiadiazole 3.15 is alkylated with a silyl group followed by treatment with CsF, ylide 3.16 is formed. This ylide ring opens allowing the endocyclic sulfur and exocyclic carbon to switch places upon ring closure. Alkylation forces loss of sulfur affording imidazole 3.17.

Scheme 3-8. Transformation of 1,2,5-thiadiazole to imidazole.

Although not a particularly useful transformation from a synthetic perspective, the transformation of 1,2,5-thiadiazole to imidazole demonstrates interesting ylide chemistry which can be interpreted as a Dimroth rearrangement with endo- and exocyclic atoms switching positions.

The real power of rearrangements in synthesis emerges in polycyclic systems. Krivapalov et al.\textsuperscript{12} reported a rearrangement yielding isoxazolopyrimidines from a terazolopyrimidine. The starting tetrazolopyrimidine 3.19 is in equilibrium with the pyrimidine azide form 3.20, presumably via a
reversible 1,3-dipolar cycloaddition. When heated, dinitrogen is eliminated from compound 3.20 to give a nitrene, 3.21, intermediate that attacks the carbonyl oxygen of the ester to afford the tetrazolopyrimidine product 3.22.

![Scheme 3-9](image)


3.4 Summary

Heterocycles have a rich chemistry both in their synthesis and in their reactivity. The Dimroth rearrangement is one of the most famous five-membered N-heterocyclic rearrangements with several variations and appearing in a number of syntheses. Novel rearrangements and mechanisms continue to be reported underscoring the activeness in this area of research. The strategic use of rearrangement reactions can afford molecular architectures otherwise difficult to access by other means.

3.5 References


Chapter 4

4 Diversity Oriented Synthesis (DOS)

4.1 Introduction

Arguably the most significant application of heterocyclic small molecules has been in the study of biological systems and in the creation of therapeutic drugs. The identification of these highly specific molecular probes is an ongoing challenge. When protein or ligand targets are known, rational design may be feasible; however, for targets that are not well characterized screening a library of compounds is the usual approach.\(^1\) With the advent of high-throughput screening (HTS), as well as advances in robotics, this process has become very efficient leaving chemists with the job of making increasingly large libraries of compounds to screen.

4.2 Combinatorial Chemistry

Combinatorial chemistry has been applied to the problem of generating libraries of compounds. This system involves the rapid generation of a large number of compounds via mixing and matching various chemical building blocks in parallel syntheses.\(^2\) Solid phase synthesis has become an invaluable part of combinatorial chemistry as a convenient means of handling and distributing chemical intermediates.

Solid phase synthesis originated as a technique for synthesized peptides.\(^3\) By performing a reaction on an insoluble solid support, the product can be “fished out” of solution after completion and washed with solvent without the need for further purification. Under these conditions an excess of reagent can be used to drive a reaction forward. This greatly simplifies a
step-by-step synthesis typically used for a peptide chain. The technique has been successfully
extended to the synthesis of small molecules.\textsuperscript{4}

The marriage of combinatorial chemistry and solid phase synthesis is exemplified in “split and
pool” synthesis.\textsuperscript{5} The methodology proceeds as follows: a resin bead-supported starting material
is split into several equal portions each of which is reacted with a different reagent. The products
of these reactions are then pooled together and split once again into equal portions and reacted
with various reagents leading to an exponential increase in the number of compounds generated.
The drawback is that all of these reactions have to be highly selective and high yielding;
otherwise, the final products end up too impure to be isolated.

The major criticism of combinatorial chemistry is that although it has been in widespread use for
well over a decade in the pharmaceutical industry, it has lead to only one FDA approved drug,
namely sorafenib. Natural products continue to be the major source of new therapeutics.\textsuperscript{6} It has
been noted that libraries of compounds generated via combinatorial chemistry lack rigidity and
chiral centers, characteristics found in many drugs because of their focus on easy chain
extending reactions at functional groups.\textsuperscript{7} Despite these criticisms, combinatorial chemistry has
been valuable in optimizing the activity profile of a compound of interest by generating a library
of related compounds to test.

4.3 Principles of Diversity Oriented Synthesis

Diversity oriented synthesis (DOS) emerged from combinatorial chemistry as a library
 generating philosophy whose central tenet is the generation of structurally diverse compounds
able to tap a larger area of chemical space.\textsuperscript{4} Chemical space is an abstract concept describing all
possible (stable) compounds that can exist in a vast “space” analogous to the universe. The
dimensions of this chemical space are chemical descriptors of a number of structural and physicochemical properties.\textsuperscript{8} Traditional combinatorial chemistry is criticized for generating libraries of compounds that exist in a very small part of chemical space. The concept of DOS, through the synthesis of structurally diverse compounds, aims to encompass a larger volume of chemical space in its libraries and in theory create a more promising source for generating lead compounds especially when screened against multiple and unrelated biological targets.\textsuperscript{9}

The guiding strategy of DOS is to employ a forward-synthetic analysis, as opposed to retro-synthesis, by starting from simple compounds and subjecting them to complexity and diversity generating reactions. This desire for structural complexity also encompasses stereo-complexity given that virtually all biological targets have some stereochemistry, a feature combinatorial chemistry has not appreciably taken advantage of. Where combinatorial chemistry’s focus is about adding functional groups; DOS is instead more focused on ring systems. This can be advantageous since rings impart rigidity onto molecules, a crucial part of highly selective compounds in biological systems.

### 4.4 Synthetic Strategies

To synthesize a DOS library, tandem reactions can be employed to quickly generate complex compounds from simple starting materials. Multi-component reactions also serve this purpose well presuming the components tolerate orthogonal functionality. Scheme 4-1 demonstrates how, in one pot, complex compounds can be generated from very simple starting materials. These starting materials can be varied easily to yield a large number of compounds.
In Scheme 4-1, a four component Ugi reaction is performed along with an intra molecular [4+2] cycloaddition to yield a complex tricyclic fused product.\textsuperscript{10,11}

In 2003, Schreiber et al.\textsuperscript{12} reported a diversity generating reaction using Grubb’s catalyst. Nearly identical substrates that contain “\(\sigma\)-elements” were directed to undergo ring closing metathesis yielding products with very different skeletal structures under a common set of reaction conditions. \(\sigma\)-Elements are appendages that pre-encode skeletal data into products. In this case, however, the \(\sigma\)-elements operated on the basis of relative stereochemistry rather than being constitutional to direct the orientation of the subsequent ring closing metathesis. This linked stereochemical control that had been richly explored by synthetic chemists to the challenge of generating skeletal diversity. Scheme 4-2 illustrates an example where stereoisomers subjected to the same reaction conditions yielded skeletally distinct products.
Scheme 4-2. σ-Element directed ring closing metathesis leading to skeletal diversification.\textsuperscript{12}

Branching pathways, where one substrate generates a number of skeletally diverse compounds, are invaluable towards generating DOS libraries. Synthetic pathways need to be strategically designed to incorporate branching points where common starting material subject to several different reaction conditions can lead to several different molecular scaffolds. A recent example by Park et al.\textsuperscript{13} shows a branching point where benzopyran 4.1, subject to various reaction conditions, can in one step access six different molecular scaffolds.
Scheme 4-3. DOS focused synthetic scheme with benzopyran as a branching point.

Although DOS sounds quite promising, it is not without its critics.\textsuperscript{14} The obvious fact remains that DOS has yet to generate a commercial drug. Smaller, simpler molecules are less specific but have a better chance of showing some activity in screening. Nonetheless, successful examples where DOS has yielded positive results are reported; for example a pyridopyrimidinone inhibitor of orthopoxviruses was identified from a DOS library.\textsuperscript{15}

4.5 Summary

With the advent of HTS and advances in robotics, synthetic chemists have been tasked with the challenge of creating large libraries of compounds to screen against biological targets.
Combinatorial chemistry was and continues to be a popular approach; however, it has been criticized for generating libraries of compounds not dissimilar enough to probe a wide area of chemical space, hence failing to maximize its chances of yielding leads for a wide variety of biological targets. DOS has emerged as a synthetic philosophy which strongly values the generation of libraries of diverse molecular scaffolds and stereochemistry via branching syntheses. Although in theory DOS addresses most of the criticisms of combinatorial chemistry in generating libraries relevant to broad biological screening, it has yet to yield a commercially available drug.

4.6 References


5 Emergence of Verdazyl Radicals as Substrates for Small Molecule Synthesis

5.1 Beginnings in Living Radical Polymerization (LRP)

Living radical polymerizations are systems where polymerization ceases not because of radical chain termination as in classical radical polymerizations but when there is no more monomer remaining. This type of system is advantageous in generating block copolymers since the addition of a different monomer enables the polymerization to restart. In order for this type of system to occur radical chain termination must be largely eliminated; not a trivial feat given that the activation energy for radical coupling is on the order of bond rotation; approximately 3-4 kcal/mol. One method of accomplishing this is with a stable radical mediating agent that can reversibly terminate the growing polymer chain. In 1993 Georges et al.\textsuperscript{1} showed that polymerization of styrene could proceed with a minimal amount of undesired termination by the addition of TEMPO to the reaction solution. The process was referred to as stable free radical polymerization (SFRP). The presence of TEMPO also served to limit the concentration of propagating radicals enabling the polymerization to be controlled to allow for predictable molecular weights and narrow molecular weight distributions. This kind of control is important for designing precision polymers.\textsuperscript{2}

Although TEMPO was successful in mediating styrene polymerizations, it was ineffective in working with acrylates. Yamada et al.\textsuperscript{3} first attempted to use 1,3,5-triphenyl verdazyl radicals as mediators for acrylate polymerizations but fell short of a successful demonstration. When 6-
oxoverdazyl radicals were used as mediators by Georges et al., they were successfully shown to control LRPs with acrylates and styrene.\textsuperscript{4}

In TEMPO mediated polymerizations, often a unimer, BST 5.1 (benzoyl styrene TEMPO trimer), is used to initiate polymerization. This unimer consists of an initiator fragment, a monomer and a TEMPO unit (figure 5-1). The same approach was applied with verdazyl radical mediated LRP with the analogous BSV unimer 5.2.

![Figure 5-1. BST (5.1) and BSV (5.2) unimers.](image)

The BSV unimer was initially synthesized by reacting verdazyl radical 5.3, styrene and BPO under a N\textsubscript{2} atmosphere for 30 min. as shown in Scheme 5-1. This synthesis, however, gave, as the major product, 5.4, which was not initially characterized, in 28\% yield and the desired BSV unimer 5.2 in only 10\% yield. The low yield problem of BSV was solved by using BST and exchanging the TEMPO with a verdazyl radical.
The Georges group considered three possible mechanisms for the formation of product 5.4. The first is based on the formation a diradical intermediate 5.6 via abstraction of a hydrogen atom by verdazyl radical 5.3, which is followed by a radical addition onto styrene (Scheme 5-2). The second proposed is a single electron transfer reaction (SET) which forms the azomethine imine 1,3-dipole 5.11 which cycloadds to styrene (Scheme 5-3). The last and eventually accepted mechanism is the hydrogen abstraction driven disproportionation of the verdazyl radical to leucoverdazyl 5.5 and an azomethine imine dipole 5.11 that undergoes a cycloaddition with styrene (Scheme 5-4).
To investigate the diradical mechanism BPO was used as a radical trap, to see if product 5.7 could be observed; none was ever shown to form. Another possible product from the hypothesized diradical mechanism was 5.8 (Figure 5-2), given that verdazyl radicals are known to couple with alkyl radicals. Again, this product was not observed either and the diradical mechanism was rejected.
The second postulated mechanism involved verdazyl radicals disproportionating via a SET to form a verdazyl radical anion 5.9 and cation 5.10 (Scheme 5-3). The cation 5.10 would then be deprotonated to afford a 1,3-dipole which undergoes subsequent cycloaddition to styrene.

Scheme 5-3. Proposed disproportionation mechanism via SET

This mechanism, however, was rejected because of the large difference between the reduction and oxidation potential of this verdazyl radical, being too great for this reaction to proceed appreciably at room temperature.6

The final and accepted mechanism again starts with a disproportionation, however, this time via a hydrogen atom abstraction facilitated by the spin polarization of the methyl hydrogens. This results in leucoverdazyl 5.5 and the azomethine imine 5.11 directly, followed by 1,3-dipolar cycloaddition. DFT calculations [B3LYP/6-31(d)] were performed by Dr. Gordon Hamer, a member of the Georges group, to ascertain the plausibility of this mechanism (Scheme 5-4).
This mechanism suggests that the maximum theoretical yield for the cycloaddition is 50% given that half of the verdazyl radicals appear to be lost as leucoverdazyl 5.5. However, when the reaction is performed under an oxygen atmosphere yields are significantly higher than 50% since under these conditions leucoverdazyl is oxidized back to the verdazyl radical, which then re-enters the reaction.  

Since leucoverdazyl oxidizes readily, even in air, to demonstrate its existence in the reaction scheme it was trapped by alkylation with benzyl bromide in the presence of sodium hydride to afford 5.12, thus, giving indirect evidence of the disproportionation reaction (Scheme 5-5).
In effect, this work demonstrated the feasibility of verdazyl radicals to be used as precursors to unique azomethine imines scaffolds which could be used in 1,3-dipolar cycloadditions.

5.3 Verdazyl Radical-Derived Azomethine Imines in 1,3-Dipolar Cycloadditions

With the generation of azomethine imines from verdazyl radicals, the door was opened to small molecule synthesis with stable radicals as substrates. The next step for Georges et al. was to investigate the scope and limitations of these cycloadditions. In 2008, the beginning of these investigations was published and the results are summarized in Table 5-1.
Table 5-1. Summary of 1,3-dipolar cycloaddition reactions with various alkene dipolarophiles. 

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dipolarophile</th>
<th>Cycloadduct</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OMe</td>
<td><img src="image" alt="Cycloadduct" /></td>
<td>74 %</td>
</tr>
<tr>
<td>2</td>
<td>O Bu</td>
<td><img src="image" alt="Cycloadduct" /></td>
<td>82 %</td>
</tr>
<tr>
<td>3</td>
<td>OMe</td>
<td><img src="image" alt="Cycloadduct" /></td>
<td>84 %</td>
</tr>
<tr>
<td>4</td>
<td>CN</td>
<td><img src="image" alt="Cycloadduct" /></td>
<td>62 %</td>
</tr>
<tr>
<td>5</td>
<td>CO2Et</td>
<td><img src="image" alt="Cycloadduct" /></td>
<td>83 %</td>
</tr>
<tr>
<td>6</td>
<td>CO2Et</td>
<td><img src="image" alt="Cycloadduct" /></td>
<td>42 %</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td><img src="image" alt="Cycloadduct" /></td>
<td>55 %</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td><img src="image" alt="Cycloadduct" /></td>
<td>40 % (82)</td>
</tr>
</tbody>
</table>
With the exception of isoprene, 1,3-dipolar cycloaddition reactions with this azomethine imine proceeded completely regioselectively with no evidence of the complementary regioisomer. Electron poor dipolarophiles resulted in the highest yields. When cycloadditions were attempted with electron-rich dipolarophiles, such as vinyl ethyl ether and N-vinyl morpholine, or with unactivated dipolarophiles, such as 1-hexene and cyclohexene, very low or no yield of cyclic products were observed. This implies that the azomethine imine dipole at work here is of the Sustmann I type given that alkenes with high energy LUMOs prove to be poor dipolarophiles.

Steric bulk did not play a major role in determining yields as seen with 5.13 (methyl acrylate case) compared to 5.14 (tert-butylacrylate case), nor did additional substituents on the α-carbon as illustrated with 5.15 (methyl methacrylate case). Due to the concertedness of this reaction, the cycloadditions with diethyl fumarate and diethyl maleate occurred stereoselectively to afford the trans 5.17 and cis 5.18 cycloadducts, respectively.

Styrene was used to study how different parameters would affect the reaction. Different solvents were tested and were found not to influence the yield to any great extent. DCM, acetone and DMSO gave yields of 45%, 51% and 53%, respectively. The highest yield was obtained when styrene was used as the solvent; however, this is likely due to a concentration effect. It was also determined that 24 h was sufficient time for the reaction and longer reaction times, 48 h and 96 h, only gave marginally better yields. Using an oxygen atmosphere for the reaction maximized the recycling of leucoverdazyl resulting in slightly higher yields as compared to simply performing the reaction in open air (63% and 52%, respectively).

In later efforts to extend the scope of alkene dipolarophiles, 1-chloroacrylonitrile, a ketene equivalent, was used in anticipation of forming the ketone product 5.22 (Scheme 5-6). The anticipated ketone product, however, was very minor (<5%) with 5.25, a double verdazyl radical
addition product, being the major product isolated. Although unexpected at first, it can be rationalized that the intermediate 5.23 readily forms since it is a stable captodative radical and then reacts with another equivalent of verdazyl radical to give intermediate 5.24, which upon loss of HCl yields the final product 5.25.

![Scheme 5-6. Reaction of verdazyl radical with a captodative alkene.](image)

No product of the 5.25 type was observed in the previous studies of alkene dipolarophiles including methyl methacrylate which could conceivably form a captodative radical in the same manner, albeit, the methyl group being only weakly donating. Two other captodative alkenes were reacted with verdazyl radical in order to observe their behaviours: 1-acetoxyacrylonitrile 5.26 and (E)-2-(methylthio)-3-phenylacrylonitrile 5.27 (Scheme 5-7).
Captodative alkene 5.26 was observed to exclusively form product 5.22 via the corresponding cycloadduct and captodative alkene 5.27 afforded its corresponding cycloadduct in modest yield. No products of the 5.25 type were observed in either case.

5.4 Verdazyl Radicals in the Synthesis of Cyclophanes

The use of verdazyl radicals as substrates in synthesis has recently and serendipitously been extended into the synthesis of macrocycles known as cyclophanes. Efforts in the Georges lab were focussed towards making verdazyl radical-based oligomers by synthesizing verdazyl radicals with dipolarophile moities on the R₃ substituent, as seen in verdazyl radical 5.29 (Scheme 5-8), in the hopes of coupling each other through cycloadditions to grow a chain. While
low molecular weight oligomers, 5.30, were observed the more interesting aspect of the reaction involved the formation of the macrocycle 5.31.\(^9\)

![Scheme 5-8. Cyclophane synthesis using verdazyl radicals.](image)

Cyclophane 5.31 was formed from an inter-molecular cycloaddition reaction to join two verdazyls together followed by an intra-molecular cycloaddition reaction to close the 12-membered ring. This reaction was followed up with the cyclophane forming tandem cycloadditions of the para-vinyl isomer of 5.29. However, the resulting cyclophane was isolated in only 3% yield, presumably due to the higher ring strain involved in the final product compared to 5.31.\(^10\)
These initial cyclophane results lead to the synthesis of other classes of cyclophanes derived from verdazyl radicals. Scheme 5-9 illustrates an example where a biphenyl extension of 5.29 was used to generate the biphenylophane 5.32.11

![Scheme 5-9. Synthesis of biphenylophane.](image)

Another route to verdazyl radical derived cyclophanes was developed using di-verdazyl radicals and bis-dipolarophiles reacting in tandem inter-intramolecular cycloaddition reactions.12 A series of 12 and 21-membered cyclophanes were synthesized and then used for structural and conformational studies (Scheme 5-10).
Scheme 5-10. Cyclophanes synthesized from di-verdazyl radicals.

5.5 Second Generation Compounds; Cycloadduct Rearrangements

The synthetic usefulness of verdazyl radicals is not limited to their cycloaddition products. The tetrahydropyrazolotetrazinones and dihydropyrazolotetrazinones that result from reactions with alkenes and alkynes, respectively, have been found to undergo a variety of rearrangements depending upon their substituents and reaction conditions. The majority of these cycloadduct rearrangements will be the topic of later chapters, however, a few examples based on the work of other lab members will be mentioned here.

During the study of the reactivities of captodative alkenes mentioned earlier in section 5.3, methyl 2-acetoxyacrylate was shown to undergo a cycloaddition reaction. The cycloadduct 5.33, however, was unstable toward elimination of acetic acid and went on to form 5.34, which incidentally is directly accessibly via an alkyne cycloaddition reaction (Scheme 5-12). Upon
heating or treatment with NaH, 5.34 underwent a Dimroth-style rearrangement to afford the pyrazolotriazinone 5.35 in 89% and 76% yield, respectively (Scheme 5-11).

![Scheme 5-11. Rearrangement of dihydropyrazolotetrazinone to pyrazolotriazinone.](image)

The rearrangement shown proceeded via loss of a methyl ester group. The mechanism of this loss is still under investigation. Our initial thoughts were that this rearrangement is driven by the aromatization of the pyrazole ring, however, an analogous rearrangement also occurred with the saturated cycloadduct tetrahydropyrazolotetrazinone, 5.36, by treatment with 2 eq. of NaH at room temperature to afford product 5.37 in 82% yield; the pre-decarboxylation rearranged product. Further treatment of 5.37 with NaH gave 5.38 (Scheme 5-12).
Scheme 5-12. Rearrangement with tetrahydropyrazolotetrazinanone.$^8$

The ease in which the saturated cycloadduct proceeded via this Dimroth-style rearrangement discredited the idea that aromatization was the driving force in the first case. A mechanism was proposed (Scheme 5-13) with accompanying DFT calculations [B3LYP/6-31G+(d,p)] showing its plausibility (Figure 5-3).
Scheme 5-13. Proposed rearrangement mechanism with tetrahydropyrazolotetrazinone.\textsuperscript{8}

Figure 5-3. DFT calculated relative energies of proposed intermediates and transition states.\textsuperscript{8}
In Scheme 5-13, enolate 5.39 attacks the carbonyl position to form 5.40 that at first may seem unlikely, however, due to the two nitrogen atoms at the ring junction, the rings can pucker towards each other enabling this interaction to occur. The resulting four membered-ring intermediate 5.40 opens the other way to yield 5.41, which effectively switches the positions of the attacking carbon with the leaving nitrogen, hence, it is a Dimroth transformation but the mechanism is unique.

When this same reaction was tried with nucleophilic primary alkoxide bases a different rearrangement resulted affording a 1,2,4-triazole 5.43 (Scheme 5-14). In this case, the nucleophilic base gets incorporated into the product.\(^{13}\)

\[\text{Scheme 5-14. Tetrahydropyrazolotetrazinone rearrangement with a nucleophilic base.}\]

5.6 Summary

From the isolation of the first 1,3-dipolar cycloaddition product of a verdazyl radical-derived azomethine imine with styrene, verdazyl radicals have emerged as useful starting materials for the synthesis of N-heterocyclic small molecules. They have been shown to react with a variety of dipolarophiles, especially electron-poor ones. This information was subsequently applied to the synthesis of a variety of unique cyclophanes. The real usefulness of verdazyl radicals in synthesis comes from access to a variety of N-heterocycles via rearrangement reactions of the cycloadducts they generate.
5.7 References


Chapter 6

6 1,3 Dipolar Cycloadditions with Verdaazy-Derived Azomethine Imines and Alkynes and Subsequent Rearrangements

6.1 Introduction and Objective

Historically, verdazyl radicals have been thought of as among the most stable radical species with no synthetically useful reactivity. What little chemistry has been reported, described in section 1.4 of this thesis, has been related to their decomposition without much explanation to the formation of the observed products. Recently, Georges et. al.\textsuperscript{1} reported a disproportionation reaction of the 1,5-dimethyl-3-phenyl-6-oxoverdazyl radical leading to a unique azomethine imine which was shown to react with alkene dipolarophiles. Electron deficient alkenes, conjugated with groups such as esters and nitriles, were observed to be particularly reactive towards this azomethine imine. The products of these cycloaddition reactions were tetrahydropyrazolotetrazinones.

This chapter describes an extension of this work in investigating the scope and limitations of using alkynes in cycloadditions with verdazyl-derived azomethine imines. Alkynes have an interesting characteristic in cycloadditions in that functionality is not destroyed. The initial cycloaddition reactions with alkenes formed a saturated pyrazolidine ring but alkynes form an unsaturated ring containing a double bond functionality to give dihydropyrazolotetrazinone cycloadducts. The most significant finding in these investigations, however, was not the isolation of the expected cycloadducts but that some of the alkyne derived cycloadducts were thermally unstable and prone to rearrangements. Generally, heterocycles are known to undergo rearrangements owing to their propensity for ring opening and bond rotation followed by ring
closure to a new compound. Two distinct rearrangement reactions were observed to occur based on the substitution pattern found on the cycloadduct and are described in this chapter.

6.2 Experimental

**Materials and Equipment:** All reagents and ACS grade solvents were purchased from Sigma-Aldrich or VWR unless otherwise stated. Column chromatography was performed with Silica Gel P60 (mesh size 40-63 µm) obtained from Silicycle. Thin layer chromatography (TLC) plates were obtained from EMD with Silica Gel 60 F254 and visualized under UV (254 nm) light. NMR spectra were recorded on a Bruker Avance III spectrometer at 23 °C, at 400 MHz for $^1$H NMR and 100 MHz for $^{13}$C NMR or on a Varian Unity INOVA-500 spectrometer at 23 °C, operating at 500 MHz for $^1$H NMR and 125 MHz for $^{13}$C NMR. Chemical shifts (δ) are reported in parts per million (ppm) referenced to tetramethylsilane (0 ppm) for $^1$H NMR spectra and CDCl$_3$ (77.0 ppm) for $^{13}$C NMR. Coupling constants (J) are reported in hertz (Hz). Spin multiplicities are indicated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Accurate mass determinations (HRMS) were carried out by the AIMS lab, Department of Chemistry, University of Toronto, using a Waters GC TOF mass spectrometer with an ESI source, MS/MS and accurate mass capabilities, associated with an Agilent 1100 capillary LC system. FT-IR spectra were acquired on a Nicolet Avatar 360 spectrometer using pellets prepared with KBr or as thin films on NaCl cells. Melting points were determined on an Electrothermal capillary melting point apparatus and are uncorrected. Single crystal X-ray structural determinations were carried out at the X-ray facility, Department of Chemistry, University of Toronto, on a Bruker-Nonius Kappa-CCD diffractometer using monochromated Mo-Kα radiation. Measurements were made using a combination of Φ and ω scans with κ offsets to fill the Ewald sphere. The data were processed using the Denzo-SMN
package. Absorption corrections were carried out using SORTAV. The structure was solved and refined using SHELXTL V6.1 for full-matrix least-squares refinement that was based on F^2. All hydrogen atoms were included in the calculated positions and allowed to refine in the riding-motion approximation with U-iso-tied to the carrier atom.

**General Cycloaddition Procedure:** 1,5-Dimethyl-3-phenyl-6-oxoverdazyl (203 mg, 1.00 mmol, 1.00 mmol) previously prepared\(^1\) was dissolved in 2 mL of THF in a 10 mL round-bottom flask. Phenyl acetylene (511 mg, 475 µL, 5.00 mmol) was added, and the solution was refluxed for 48 h. The reaction solution was cooled to ambient temperature and the unreacted styrene was removed in vacuo. The product was isolated by silica column chromatography (1:2 ethyl acetate/hexanes).

**2-Methyl-4,6-diphenyl-2,8-dihydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (6.1)**

![Structure of 2-Methyl-4,6-diphenyl-2,8-dihydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one](image)

1,5-Dimethyl-3-phenyl-6-oxoverdazyl (203 mg, 1.00 mmol) was reacted according to the general procedure for cycloaddition with the addition of CuI (19 mg, 0.1 eq.) to yield a yellow oil (39 mg, 13%); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.37-7.34 (d, \(J = 7.5\) Hz, 2H), 7.13-7.08 (m, 3H), 7.07-6.99 (m, 5H), 5.12-5.10 (t, \(J = 2.5\) Hz, 1H), 4.76-4.74 (d, \(J = 2.0\) Hz, 2H), 3.38 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 158.7, 146.2, 141.5, 130.6, 130.1, 129.8, 128.7, 128.2, 127.93, 127.88, 127.5, 101.5, 51.4, 36.8; HRMS (ESI): \(m/z\) [M]^+ calc’d for C\(_{18}\)H\(_{16}\)N\(_4\)O 304.1324, found 304.1327.
Dimethyl 2-methyl-1-oxo-4-phenyl-2,8-dihydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazine-6,7-dicarboxylate (6.2)

![Chemical Structure](image)

1,5-Dimethyl-3-phenyl-6-oxoverdazyl (203 mg, 1.00 mmol) was reacted with dimethyl acetylene dicarboxylate according to the general procedure for cycloaddition to yield a yellow oil (155 mg, 45%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.63-7.59 (d, $J = 7.2$ Hz, 2H), 7.51-7.46 (t, $J = 7.25$ Hz, 1H), 7.44-7.38 (t, $J = 7.3$ Hz, 2H), 4.84 (s, 2H), 3.71 (s, 3H), 3.38 (s, 3H), 3.25 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 161.7, 159.2, 156.9, 141.6, 140.1, 131.5, 129.1, 128.5, 127.9, 104.5, 52.7, 51.7, 51.2, 37.2; HRMS (ESI): $m$/z [M+H]$^+$ calc’d for C$_{16}$H$_{17}$N$_4$O$_5$ 345.1193, found 345.1203.

Methyl 2-methyl-1-oxo-4-phenyl-2,8-dihydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazine-6-carboxylate (6.3)

![Chemical Structure](image)

1,5-Dimethyl-3-phenyl-6-oxoverdazyl (203 mg, 1.00 mmol) was reacted with methyl propiolate according to the general procedure for cycloaddition to yield a yellow oil (89 mg, 31%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.59-7.55 (m, 2H), 7.43-7.38 (m, 3H), 5.92-5.89 (t, $J = 2.7$ Hz, 1H), 4.71-4.69 (d, $J = 2.7$ Hz, 2H), 3.34 (s, 3H), 3.30 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 159.0,
146.1, 134.2, 131.7, 130.4, 129.4, 128.6, 127.1, 113.3, 52.0, 51.3, 36.8; HRMS (ESI): \textit{m/z} [M+H]^+ \text{calc'd for C}_{14}H_{14}N_4O_3 287.1125, \text{found} 287.1138.

\textbf{2-Methyl-4-phenyl-6-(trimethylsilyl)-2,8-dihydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (6.4)}

![Image of 2-Methyl-4-phenyl-6-(trimethylsilyl)-2,8-dihydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one](image)

1,5-Dimethyl-3-phenyl-6-oxoverdazyl (203 mg, 1.00 mmol) was reacted with ethynyl trimethyl silane according to the general procedure for cycloaddition to yield a yellow oil (24 mg, 8%); \textit{^1}H NMR (400 MHz, CDCl$_3$) \(\delta\) 7.74-7.71 (d, J = 7.3 Hz, 2H), 7.50-7.40 (m, 3H), 5.23-5.21 (t, J = 2.4 Hz, 1H), 4.46-4.45 (d, J = 2.4 Hz, 2H), 3.36 (s, 3H), -0.19 (s, 9H); \textit{^13}C NMR (100 MHz, CDCl$_3$) \(\delta\) 159.4, 147.1, 145.7, 131.8, 131.2, 128.9, 128.7, 115.5, 51.6, 37.2, -1.2; MS (TOF EI\(^+\)): \textit{m/z} [M\(^+\)] \text{for C}_{15}H_{20}N_4O_Si 300.1.

\textbf{2-Methyl-4-phenyl-6-tosyl-2,8-dihydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (6.5)}

![Image of 2-Methyl-4-phenyl-6-tosyl-2,8-dihydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one](image)

1,5-Dimethyl-3-phenyl-6-oxoverdazyl (203 mg, 1.00 mmol) was reacted with ethynyl p-tolyl sulfone according to the general procedure for cycloaddition to yield a yellow oil (237 mg, 62%);
$^1$H NMR (400 MHz, CDCl$_3$) δ 7.75-7.72 (d, J = 8.4 Hz, 2H), 7.13-7.08 (m, 3H), 7.59-7.52 (m, 3H), 7.50-7.45 (m, 2H), 7.37-7.33 (d, J = 8.2 Hz, 2H), 7.09-7.08 (t, J = 1.4 Hz, 1H), 4.75-4.73 (d, J = 1.4 Hz, 2H), 3.28 (s, 3H), 2.45 (s, 3H);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 154.5, 144.6, 141.2, 136.6, 133.7, 131.8, 130.0, 129.2, 128.1, 127.7, 127.2, 112.8, 51.4, 36.8, 21.5; HRMS (ESI): m/z [M]$^+$ calc’d for C$_{19}$H$_{18}$N$_4$O$_3$S 382.1100, found 382.1089.

**Ethyl 2-methyl-1-oxo-4,6-diphenyl-2,8-dihydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazine-7-carboxylate (6.6)**

1,5-Dimethyl-3-phenyl-6-oxoverdazyl (203 mg, 1.00 mmol) was reacted with ethyl phenyl propiolate according to the general procedure for cycloaddition to yield a yellow oil (68 mg, 18%); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.33-7.29 (d, J = 7.1 Hz, 2H), 7.18-7.10 (m, 5H), 4.94 (s, 2H), 4.08-4.02 (q, J = 7.1 Hz, 2H), 3.44 (s, 3H), 1.13-1.08 (t, J = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 162.7, 158.8, 149.1, 143.8, 130.2, 130.0, 129.7, 129.6, 127.8, 127.5, 127.4, 126.9, 101.9, 59.8, 51.7, 37.3, 13.9; HRMS (ESI): m/z [M]$^+$ calc’d for C$_{21}$H$_{20}$N$_4$O$_3$ 376.1535, found 376.1531.

**6-Acetyl-2-methyl-4-phenyl-2,8-dihydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (6.7)**

1,5-Dimethyl-3-phenyl-6-oxoverdazyl (203 mg, 1.00 mmol) was reacted with ethyl phenyl propiolate according to the general procedure for cycloaddition to yield a yellow oil (68 mg, 18%); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.33-7.29 (d, J = 7.1 Hz, 2H), 7.18-7.10 (m, 3H), 7.09-7.02 (m, 5H), 4.94 (s, 2H), 4.08-4.02 (q, J = 7.1 Hz, 2H), 3.44 (s, 3H), 1.13-1.08 (t, J = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 162.7, 158.8, 149.1, 143.8, 130.2, 130.0, 129.7, 129.6, 127.8, 127.5, 127.4, 126.9, 101.9, 59.8, 51.7, 37.3, 13.9; HRMS (ESI): m/z [M]$^+$ calc’d for C$_{21}$H$_{20}$N$_4$O$_3$ 376.1535, found 376.1531.
1,5-Dimethyl-3-phenyl-6-oxoverdazyl (203 mg, 1.00 mmol) was reacted with 3-butyn-2-one according to the general procedure for cycloaddition to yield a yellow oil (51 mg, 19%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.59-7.56 (m, 2H), 7.42-7.37 (m, 3H), 5.90-5.88 (t, \(J = 2.9\) Hz, 1H), 4.71-4.70 (d, \(J = 3.0\) Hz, 2H), 3.34 (s, 3H), 2.15 (s, 3H); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 187.6, 158.5, 146.3, 142.0, 132.1, 130.3, 128.4, 126.9, 114.5, 51.1, 36.7, 27.1.

**Ethyl 2,7-dimethyl-1-oxo-4-phenyl-2,8-dihydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazine-6-carboxylate (6.8)**

![Chemical Structure](image)

1,5-Dimethyl-3-phenyl-6-oxoverdazyl (203 mg, 1.00 mmol) was reacted with ethyl 2-butynoate according to the general procedure for cycloaddition to yield a yellow oil (38 mg, 12%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.56-7.52 (m, 2H), 7.42-7.36 (m, 3H), 4.59-4.57 (q, \(J = 1.6\) Hz, 2H), 3.68-3.62 (q, \(J = 7.2\) Hz, 2H), 3.32 (s, 3H), 2.07-2.05 (t, \(J = 1.6\) Hz, 3H), 0.86-0.82 (t, \(J = 7.2\) Hz, 3H).

**6-(2,4-Difluorophenyl)-2-methyl-4-phenyl-7-(trimethylsilyl)-2,8-dihydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (6.9)**
1,5-Dimethyl-3-phenyl-6-oxoverdazyl (203 mg, 1.00 mmol) was reacted with (2,4-
difluorophenylethynyl)trimethyilsilane according to the general procedure for cycloaddition to
yield a yellow oil (45 mg, 11%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.41-7.38 (d, $J = 7.5$ Hz, 2H),
7.20-7.16 (tt, $J = 7.4$, 1.4 Hz, 1H), 7.12-7.07 (tt, $J = 7.6$, 1.4 Hz, 2H), 6.99-6.92 (m, 1H), 6.59-
6.53 (m, 1H), 6.44-6.38 (td, $J = 9.2$, 2.4 Hz, 1H), 4.72 (s, 2H), 3.41 (s, 3H), -0.08 (s, 9H); $^{13}$C
NMR (100 MHz, CDCl$_3$) $\delta$ 158.0, 144.3, 140.9, 133.1-133.0 (dd $J = 9.8$, 3.9 Hz), 131.4, 130.3,
127.9-127.8 (d, $J = 9.5$ Hz), 112.6, 111.0, 110.7 (dd, $J = 21.1$, 3.6 Hz), 103.9-103.4 (t, $J = 25.8$
Hz), 56.3, 37.3, -1.3; HRMS (ESI): $m/z$ [M+H]$^+$ calc’d for C$_{21}$H$_{23}$N$_4$OF$_2$Si 413.1603, found
413.1610.

**Di-tert-butyl 2-methyl-1-oxo-4-phenyl-2,8-dihydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazine-
6,7-dicarboxylate (6.10)**

1,5-Dimethyl-3-phenyl-6-oxoverdazyl (203 mg, 1.00 mmol) was reacted with di-tert-butyl
acetylene dicarboxylate according to the general procedure for cycloaddition yield a yellow oil
(240 mg, 56%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.71-7.67 (d, $J = 7.0$ Hz, 2H), 7.48-7.38 (m, 3H), 4.73 (s, 2H), 3.38 (s, 3H), 1.46 (s, 9H), 1.06 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 160.6, 157.4, 157.2, 142.5, 140.3, 131.3, 129.9, 128.7, 127.7, 106.9, 84.8, 81.3, 51.3, 37.1, 28.0, 26.9; HRMS (ESI): $m/z$ [M+H]$^+$ calc’d for C$_{22}$H$_{29}$N$_4$O$_5$ 429.2132, found 429.2149.

Diethyl 2-methyl-1-oxo-4-phenyl-2,8-dihydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazine-6,7-dicarboxylate (6.11)

1,5-Dimethyl-3-phenyl-6-oxoverdazyl (203 mg, 1.00 mmol) was reacted with diethyl acetylene dicarboxylate according to the general procedure for cycloaddition to yield a yellow oil (219 mg, 59%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.65-7.61 (d, $J = 7.2$ Hz, 2H), 7.50-7.45 (t, $J = 7.4$ Hz, 1H), 7.43-7.37 (t, $J = 7.6$ Hz, 2H), 4.83 (s, 2H), 4.20-4.13 (q, $J = 7.1$ Hz, 2H), 3.68-3.61 (q, $J = 7.1$ Hz, 2H), 3.38 (s, 3H), 1.26-1.21 (t, $J = 7.1$ Hz, 3H), 1.03-0.98 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 161.3, 158.8, 156.3, 141.7, 140.2, 131.5, 129.2, 128.5, 128.0, 104.7, 62.6, 60.6, 51.2, 37.2, 14.0, 13.2; HRMS (ESI): $m/z$ [M+H]$^+$ calc’d for C$_{18}$H$_{21}$N$_4$O$_5$ 373.1506, found 373.1497.

2-Methyl-4,7-diphenyl-2,8-dihydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (6.12)
1,5-Dimethyl-3-phenyl-6-oxoverdazyl (203 mg, 1.00 mmol) was reacted with *alpha*-bromostyrene according to the general procedure for cycloaddition to yield a yellow oil (49 mg, 16%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.62-7.58 (m, 4H), 7.55-7.44 (m, 4H), 7.42-7.37 (m, 2H), 6.95-6.93 (t, $J = 1.0$ Hz, 1H), 5.05-5.04 (d, $J = 1.1$ Hz, 2H), 3.36 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 187.8, 155.3, 141.1, 138.9, 135.3, 131.7, 131.5, 129.1, 128.5, 127.7, 127.6, 114.0, 52.7 36.9.

7-Benzoyl-2-methyl-4,6-diphenyl-2,8-dihydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (6.13)

1,5-Dimethyl-3-phenyl-6-oxoverdazyl (203 mg, 1.00 mmol) was reacted with 2-benzoyl-1-phenylacetylene according to the general procedure for cycloaddition to yield a yellow oil (94 mg, 23%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.32-7.28 (d, $J = 7.7$ Hz, 2H), 7.24-7.20 (d, $J = 7.6$ Hz, 2H), 7.11-7.04 (m, 2H), 7.02-6.97 (t, $J = 7.8$ Hz, 2H), 6.96-6.91 (t, $J = 7.7$ Hz, 2H), 6.87-6.80 (m, 3H), 6.76-6.71 (t, $J = 7.4$ Hz, 2H), 5.12 (s, 2H), 3.50 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 190.2, 158.5, 149.3, 138.5, 130.6, 130.3, 129.9, 129.8, 129.7, 128.1, 127.8, 127.5, 127.4, 127.3, 126.8, 111.5, 52.8, 37.5.

1-Methyl-3-[phenyl(5-phenyl-1H-pyrazol-1-yl)methylene]urea (6.14)
Compound 6.1 (100 mg) was dissolved in 10 mL of toluene in a 25 mL round-bottom flask and heated at 90 °C for 3 days. The product was isolated by silica column chromatography (1:3 ethyl acetate/hexanes) to yield a yellow oil (82 mg, 82%); ¹H NMR (400 MHz, CDCl₃) δ 7.87-7.86 (d, J = 1.8 Hz, 1H), 7.39-7.35 (m, 2H), 7.29-7.22 (m, 3H), 7.19-7.12 (m, 5H), 6.63-6.62 (d, J = 1.8 Hz, 1H), 5.74-5.68 (q, J = 4.5 Hz, 1H), 3.09-3.07 (d, J = 4.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 144.5, 142.1, 134.3, 132.8, 131.4, 128.84, 128.80, 128.6, 128.5, 128.1, 127.9, 127.0, 125.4, 124.6, 105.7, 37.7.

1-((4,5-Diphenyl-1H-pyrazol-1-yl)(phenyl)methylene)-3-methylurea (6.15)

1,5-Dimethyl-3-phenyl-6-oxoverdazyl (203 mg, 1.00 mmol) was reacted with diphenylacetylene according to the general procedure for cycloaddition except dissolved in toluene and refluxed at 110 °C for 3 days. The product was isolated by silica column chromatography (1:30 ethyl acetate/toluene) to yield a yellow oil (19 mg, 5%); ¹H NMR (400 MHz, CDCl₃) δ 8.05 (s, 1H), 7.30-7.27 (m, 4H), 7.25-7.12 (m, 11H), 5.82-5.77 (q, J = 4.5 Hz, 1H), 3.09-3.07 (d, J = 4.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 141.6, 140.7, 134.6, 132.7, 132.2, 129.0, 128.9, 128.63,
128.60, 128.5, 128.1, 128.0, 127.8, 126.7, 124.8, 121.1, 37.8; HRMS (ESI): m/z [M]+ calc’d for C_{24}H_{22}N_4O 380.1637, found 380.1656.

5-(1,2-Diphenylvinyl)-2,4-dimethyl-6-phenyl-4,5-dihydro-1,2,4,5-tetrazin-3(2H)-one (6.16)

1,5-Dimethyl-3-phenyl-6-oxoverdazyl (203 mg, 1.00 mmol) was reacted with diphenylacetylene according to the general procedure for cycloaddition except that the reagents were dissolved in toluene and refluxed at 110 °C for 3 days. The product was isolated by silica column chromatography (1:30 ethyl acetate/toluene) to yield a yellow oil (65 mg, 17%); 1H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.94-7.90 (m, 2H), 7.42-7.33 (m, 8H), 7.01-6.97 (m, 3H), 6.75-6.71 (m, 2H) 5.97 (s, 1H), 3.42 (s, 3H), 2.84 (s, 3H); 13C NMR (100 MHz, CDCl\textsubscript{3}) δ 157.6, 145.6, 141.9, 135.3, 134.2, 131.2, 130.5, 130.2, 128.8, 128.62, 128.57, 128.2, 127.8, 126.5, 126.2, 115.6, 38.1, 37.1.

Ethyl 1-(((methylcarbamoyl)imino)(phenyl)methyl)-5-phenyl-1H-pyrazole-4-carboxylate (6.17)
Compound 6.6 (100 mg) was dissolved in 10 mL of xylenes in a 25 mL round-bottom flask and heated at 130 °C for 2 days. The product was isolated by silica column chromatography (1:2 ethyl acetate/hexanes) to yield a yellow oil (68 mg, 68%); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.32 (s, 1H), 7.33-7.22 (m, 5H), 7.16-7.08 (m, 5H), 5.70-5.65 (q, J = 4.4 Hz, 1H), 4.28-4.21 (q, J = 7.2 Hz, 2H), 3.09-3.07 (d, J = 4.5 Hz, 3H), 1.27-1.23 (t, J = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 162.5, 147.1, 144.2, 133.7, 131.5, 129.6, 129.2, 128.1, 128.0, 127.7, 127.0, 124.5, 112.6, 60.2, 37.7, 14.0; HRMS (ESI): m/z [M]+ calc’d for C$_{24}$H$_{22}$N$_4$O 376.1535, found 176.1544.

1-((5-(2,4-Difluorophenyl)-4-(trimethylsilyl)-1H-pyrazol-1-yl)(phenyl)methylene)-3-methylurea (6.18)

Compound 6.9 (40 mg) was dissolved in 10 mL of toluene in a 25 mL round-bottom flask and heated at 90 °C for 3 days. The product was isolated by silica column chromatography (1:3 ethyl acetate/hexanes) to yield a yellow oil (22 mg, 55%); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.86 (s, 1H), 7.19-7.09 (m, 5H), 7.05-6.98 (m, 1H), 6.75-6.65 (m, 2H), 5.84 (br, 1H), 3.07 (s, 3H), 0.10 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) 147.0, 141.3, 134.6, 132.5-132.4 (dd J = 9.9, 3.6 Hz), 132.1, 128.1, 124.8, 116.7, 111.3-111.1 (d, J = 21.4, 3.6 Hz), 104.1-103.6 (t, J = 25.8 Hz), 37.8, -0.6.

1-((4-Benzoyl-5-phenyl-1H-pyrazol-1-yl)(phenyl)methylene)-3-methylurea (6.19)
Compound 6.13 (100 mg) was dissolved in 10 mL of xylenes in a 25 mL round-bottom flask and heated at 130 °C for 3 days. The product was isolated by silica column chromatography (1:3 ethyl acetate/hexanes) to yield a yellow oil (72 mg, 72%); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.22 (s, 1H), 7.81-7.78 (d, J = 7.3 Hz, 2H), 7.52-7.47 (t, J = 7.5 Hz, 1H), 7.40-7.35 (t, J = 7.9 Hz, 2H), 7.26-7.22 (m, 2H), 7.20-7.12 (m, 8H), 5.78-5.73 (q, J = 4.4 Hz, 1H), 3.13-3.10 (d, J = 4.4 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 189.5, 147.1, 144.5, 138.2, 133.7, 132.4, 131.5, 129.5, 129.3, 129.0, 128.9, 128.12, 128.08, 128.0, 127.2, 125.1, 124.5, 119.9, 37.8.

N,2,4-trimethyl-3-oxo-6-phenyl-N’-(phenyl(5-phenyl-1H-pyrazol-1-yl)methylene)-3,4-dihydro-1,2,4,5-tetrazine-1(2H)-carbohydrazide (6.20)

1,5-Dimethyl-3-phenyl-6-oxoverdazyl (1.00 g, 4.93 mmol) was reacted according to the general procedure for cycloaddition using toluene rather than THF. The reaction solution was heated at 80 °C for a week. The product was isolated by silica column chromatography (1:2 ethyl acetate/hexanes) to yield a yellow oil (225 mg, 9%); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.71-7.70 (d, J = 1.8 Hz, 1H), 7.51-7.46 (d, J = 7.3 Hz, 2H), 7.35-7.30 (t, J = 7.3 Hz, 1H), 7.27 (br, 5H), 7.25-
7.18 (m, 5H), 7.12-7.08 (d, J = 7.7 Hz, 2H), 6.55-6.53 (d, J = 1.8 Hz, 1H), 3.37 (s, 3H), 3.23 (s, 3H), 2.78 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 158.7, 155.9, 145.8, 144.3, 141.9, 139.1, 134.0, 131.1, 130.5, 129.9, 128.9, 128.8, 128.4, 128.20, 128.18, 127.3, 126.8, 125.9, 106.8, 37.7, 37.2, 35.0; HRMS (ESI): m/z [M+H]$^+$ calc’d for C$_{28}$H$_{27}$N$_8$O$_2$ 507.2251, found 507.2239.

(E)-N,2,4-trimethyl-3-oxo-N'-(5-phenyl-1H-pyrazol-1-yl)methylene)-3,4-dihydro-1,2,4,5-tetrazine-1(2H)-carbohydrazide (6.21)

1,5-Dimethyl-6-oxoverdazyl (300 mg, 2.36 mmol) was reacted according to the general procedure for cycloaddition except using toluene rather than THF. The reaction solution was heated at 80 °C for a week. The product was isolated by silica column chromatography (1:3 ethyl acetate/hexanes) to yield a yellow oil (67 mg, 8%); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.05 (s, 1H), 7.77-7.76 (d, J = 1.6 Hz, 1H), 7.51 (s, 1H), 7.50-7.47 (m, 3H), 7.46-7.41 (m, 2H), 6.48-6.47 (d, J = 1.7 Hz, 1H), 3.32 (s, 3H), 3.20 (s, 3H), 3.16 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 157.0, 153.3, 144.3, 142.6, 133.0, 130.1, 129.4, 129.1, 129.0, 128.9, 109.4, 36.6, 34.6, 31.2; HRMS (ESI): m/z [M+H]$^+$ calc’d for C$_{28}$H$_{27}$N$_8$O$_2$ 507.2251, found 507.2239.

1-Methyl-2-phenylpyrazolo[1,5-d][1,2,4]triazinone (6.22)
Compound 6.3 (200 mg, 0.69 mmol) was dissolved in 10 mL of THF and refluxed for 3 h. The product was isolated by silica column chromatography (1:3 ethyl acetate/hexanes) to yield a white solid (139 mg, 89%): mp 119-121 °C; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.12-8.09 (m, 2H), 8.02-8.01 (d, J = 2.0 Hz, 1H), 7.57-7.52 (m, 3H), 7.23-7.22 (d, J = 2.0 Hz, 1H), 3.82 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 153.7, 143.7, 138.5, 134.6, 131.0, 129.4, 128.8, 128.4, 106.5, 37.9; HRMS (EI): m/z [M+H]$^+$ calc’d for C$_{12}$H$_{11}$N$_4$O 227.0929, found 227.0927.

1-Methyl-2-phenyl-9-(methylcarboxylate)pyrazolo[1,5-d][1,2,4]triazinone (6.23)

Compound 6.2 (110 mg, 0.32 mmol) was heated neat at 150 °C for 2 days. The product was isolated by silica column chromatography (1:3 ethyl acetate/hexanes) to yield a white solid (45 mg, 50%); m.p. 100–103 °C. Unreacted starting material (47 mg, 42%) was recovered. $^1$H NMR (400 MHz, CDCl$_3$): δ 8.37 (s, 1H), 8.05-8.03 (m, 2H), 7.57-7.52 (m, 3H), 3.98 (s, 3H), 3.84 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 161.5, 151.9, 145.7, 138.2, 133.2, 131.2, 129.6, 128.5, 128.3, 114.8, 52.5, 38.5; HRMS (EI): m/z [M]$^+$ calc’d for C$_{14}$H$_{12}$N$_4$O$_3$ 345.1193, found 345.1203.

1-Methyl-2-phenyl-9-(ethylcarboxylate)pyrazolo[1,5-d][1,2,4]triazinone (6.24)
Compound 6.11 (175 mg, 0.47 mmol) was heated neat at 150 °C for 2 days. The product was isolated by silica column chromatography (1:3 ethyl acetate/hexanes) to yield a white solid (24 mg, 17%); m.p. 104–105 °C; Unreacted starting material (123 mg, 62%) was recovered. $^1$H NMR (400 MHz, CDCl$_3$): δ 8.36 (s, 1H), 8.05-8.03 (m, 2H), 7.60-7.51 (m, 3H), 4.48-4.42 (q, J = 7.2 Hz, 2H), 3.84 (s, 3H), 1.46-1.42 (t, J = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 160.9, 151.7, 145.4, 138.0, 133.0, 131.0, 129.4, 128.30, 128.27, 115.2, 61.4, 38.4, 14.1.

6.3 Results and Discussion

To expand the verdazyl radical chemistry, alkynes were used as another class of dipolarophiles to undergo 1,3-dipolar cycloaddition reactions with the verdazyl derived azomethine imine. The alkyne analog of styrene, phenyl acetylene, was used to form cycloadduct 6.1 (Table 6.1). In contrast to the moderate cycloaddition yield of 63% reported with styrene, phenyl acetylene afforded a poor 11% yield of cycloadduct even with a prolonged reaction time of three days. In an effort to improve the yield metal catalysis was employed in the cycloaddition reaction.

Recent reports in the literature suggested gold as a good candidate for catalysis due to its "alkynophilic" properties as a Lewis acid in cycloaddition reactions$^2$, as well as other transformations.$^3$ AuCl$_3$, as well as Me$_3$PAuCl were chosen as catalysts. The cycloaddition reactions were repeated using these catalysts under various conditions, however, no improvement in yield was observed.
Copper catalysis was reported to improve yields significantly in 1,3-dipolar cycloaddition reactions with alkynes in systems where virtually no product was formed due to the energetically inaccessible HOMO/ LUMO pairing as described by the Sustmann II system. This approach envisioned the opposite electronic effect intended with the gold catalysis. Instead of lowering the LUMO of the dipolarophile to make it more accessible to the HOMO of the dipole, the HOMO of the dipolarophile was to be raised to the point of making a favourable interaction with the LUMO of the dipole to create, in effect, a Sustmann III system. Copper (I) iodide, at 10 mol% catalyst loading, gave a marginally better yield of 13% of 6.1. A likely reason for inability of Cu to improve the yield of the cycloaddition reaction is that the verdazyl radical itself, as well as other species present in solution, can complex with Cu in the reaction mixture via their nitrogen atoms and sequester it away, thus preventing any catalysis.

Reaction yields with other alkyne dipolarophiles, especially those with electron withdrawing substituents such as ester group, were higher albeit still modest. The best cycloaddition yield was observed with a sulfone substituted, forming product 6.5 in 62% yield. The results of other cycloaddition reactions with the dimethyl-3-oxy-verdazyl-derived azomethine imine with alkyne dipolarophiles are summarized in Table 6-1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dipolarophile</th>
<th>Cycloadduct</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td><img src="image" alt="Cycloadduct Diagram" /></td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
<td>Reaction Scheme</td>
<td>Yield</td>
</tr>
<tr>
<td>---</td>
<td>-------------------</td>
<td>-----------------</td>
<td>-------</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Structure 2" /></td>
<td><img src="image" alt="Scheme 2" /></td>
<td>45%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Structure 3" /></td>
<td><img src="image" alt="Scheme 3" /></td>
<td>31%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Structure 4" /></td>
<td><img src="image" alt="Scheme 4" /></td>
<td>8%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Structure 5" /></td>
<td><img src="image" alt="Scheme 5" /></td>
<td>62%</td>
</tr>
<tr>
<td>6</td>
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<tr>
<td>7</td>
<td><img src="image" alt="Structure 7" /></td>
<td><img src="image" alt="Scheme 7" /></td>
<td>19%</td>
</tr>
</tbody>
</table>
Table 6-1. Verdazyl derived azomethine imine cycloadditions with alkynes.

As with the previously described cycloaddition reactions with alkenes, the alkyne reactions occurred regioselectively. Entry 12 was an attempt at using α-bromo styrene to perform a high yielding cycloaddition followed by loss of HBr to generate 6.1 for further study of its rearrangement properties. The intended reaction did not proceed in high yield, however the product 6.12 interestingly displayed the opposite regioselectivity of all the other dipolarophiles used where typically the C6-position is left unsubstituted.

Upon sitting at room temperature for a week compound 6.1 disappeared. A TLC showed only one new spot above where 6.1 should have been suggesting it was decomposing cleanly into a slightly less polar compound. This process was greatly accelerated with heating. Compound 6.1 completely converted into this new compound when heated at 90 °C for three days. This new compound was an oil and using only ¹H and ¹³C NMR and MS data structure 6.25 was proposed (Scheme 6-1).

![Scheme 6-1](image)

**Scheme 6-1.** Erroneous proposed rearrangement structure.

A rearrangement was envisioned involving a cleavage of the N-N bond at the ring junction of 6.1 to afford 6.25. This type of structure had not been previously reported and analogous
rearrangements were observed with other alkyne cycloadducts containing an aryl substituent at the C6-position. The proposed structure remained unconfirmed until attempts at crystallizing the ammonium salt succeeded in allowing X-ray diffraction characterization of the rearranged product. The correct structure turned out to be 6.14 (Table 6-2) where the rearrangement results are summarized.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cycloadduct</th>
<th>Rearrangement Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="6.1" /></td>
<td><img src="image" alt="6.14" /></td>
<td>82%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="6.26" /></td>
<td><img src="image" alt="6.15" /></td>
<td>5% (over 2 steps)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="6.6" /></td>
<td><img src="image" alt="6.17" /></td>
<td>68%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="6.9" /></td>
<td><img src="image" alt="6.18" /></td>
<td>55%</td>
</tr>
</tbody>
</table>
Table 6-2. Summary of rearrangement products involving 6-aryl substituted cycloadducts.

These rearrangements occurred in reasonably high yield with the exception of entry 2. The cycloaddition reaction with diphenyl acetylene proved difficult and only through forcing conditions (refluxing toluene for 48 h), presumably occurring via the cycloadduct which was never isolated, were we able to isolate the rearranged product. Interestingly, a small amount of a direct addition reaction by the verdazyl radical was observed to occur to give 6.16, a similar reaction product seen once before with captodative alkenes as discussed in section 5.3. The results of this reaction are shown in Scheme 6-2.

Scheme 6-2. Cycloaddition reaction results with 1,5-dimethyl-3-phenyl-6-oxoverdazyl radical and diphenyl acetylene.

Since the discovery of the true structure of the rearranged product, further work was abandoned given that it amounted to a low yielding multi-step synthesis of pyrazoles. Although the transformation is interesting, it is of limited synthetic usefulness. A mechanism has not been
proposed although experiments meant to generate the rearranged product \textit{in situ} via prolonged cycloaddition conditions at 80 °C resulted in structures 6.20 and 6.21 (Scheme 6-3).

![Scheme 6-3](image)

**Scheme 6-3.** Reactions of phenyl acetylene with 1,5-dimethyl-3-phenyl-6-oxoverdazyl radical under prolonged cycloaddition conditions.

The product structures, 6.20 and 6.21 were confirmed by single crystal X-ray crystallography. Unlike with rearrangement product 6.14, both hydrazide chains found in the starting material 6.1 are still intact. It can be hypothesized that the N-methyl nitrogen in 6.1 is translocated via an isocyanate intermediate (Figure 6-1) via a transformation akin to a Hofmann rearrangement. Without first isolating 6.1 and instead allowing the rearrangement to occur in the presence of leucoverdazyl, it is likely such an intermediate was nucleophilically attacked and trapped to afford 6.20 and 6.21.

![Figure 6-1](image)

**Figure 6-1.** Hypothesized intermediate deduced from compounds 6.20 and 6.21.
A second type of rearrangement observed with verdazyl radical derived alkyne cycloadducts was discussed in section 5.5 of this thesis. It occurs with cycloadducts that have an ester functionality as the 6-position and hence acidic hydrogens on the pyrazolo- ring. This rearrangement, which occurred slowly at room temperature, was first observed with compound \textbf{6.3} (Scheme 6-4) and resulted in the formation of \textbf{6.22}. Heating compound \textbf{6.3} in THF at reflux for 3 h gave complete conversion to \textbf{6.22} in 89\% yield. Addition of excess NaH to a solution of \textbf{6.3} in THF at room temperature greatly increased the rate of rearrangement leading to complete conversion within an hour. The mechanism for the rearrangement is shown in Scheme 6-4.

![Scheme 6-4. Rearrangement mechanism for ester substituted alkyne cycloadducts](image)

The details of the last step regarding the loss of the ester group are still unknown and working out that part of the mechanism is an ongoing project. This rearrangement was also observed for compounds \textbf{6.2} and \textbf{6.11}. In these cases higher temperature were necessary for the reactions to proceed. Both compounds were heated at 150 °C for two days. Cycloadduct \textbf{6.2} afforded a 42\% yield of \textbf{6.23} with a 50\% recovery of the starting material. Cycloadduct \textbf{6.11}, which is even more
sterically hindered, gave only 17% of 6.24 with 62% of recovered starting material. The di-ester cycloadducts did not react cleanly when exposed to excess NaH as was the case with 6.3, instead several unidentified compounds were produced with no anticipated rearranged product. The di-tert-butyl di-ester 6.10 was unreactive towards heating and did not show any rearranged product. The results of these rearrangements are summarized in Table 6-3.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cycloadduct</th>
<th>Rearrangement Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td>89%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
<td>42% with 50% starting material recovered</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
<td>17% with 62% starting material recovered</td>
</tr>
</tbody>
</table>

Table 6-3. Summary of rearrangements involving 6-ester substituted cycloadducts.

6.4 Summary

In an effort to expand the range of dipolarophiles with which verdazyl radical derived azomethine imines react, cycloaddition reactions were performed with various alkynes to produce dihydropyrazoloterazinone cycloadducts. The reaction yields experienced with alkynes were lower than those with alkene dipolarophiles but the familiar pattern of electron deficient
dipolarophiles being more reactive was once again observed. Metal catalysis proved ineffective in improving reaction yields, which were typically low, since the metal likely coordinated with the verdazyl radical rather than the dipolarophiles thus nullifying the effect of the catalysis. The cycloadducts derived from the alkyne cycloaddition reaction, however, showed interesting properties towards rearrangement. Cycloadducts with aryl groups at the C6-position underwent a rearrangement which generated a substituted pyrazole ring. Alternatively, cycloadducts with ester groups at that position underwent a rearrangement and decarboxylation to afford pyrazolotriazinones. The propensity of these cycloadducts to rearrange opened up a new area of research in the Georges lab towards generating second generation scaffolds from verdazyl radicals which will be a topic of the next chapter.

6.5 References

Chapter 7

7 Synthesis of 3-Methyl-5-Aryl-1,3,4-Oxadiazolones by Rearrangement of Verdazyl-Derived Cycloadducts

7.1 Introduction and Objective

In chapter 6, verdazyl radical derived azomethine imines were shown to undergo cycloaddition reactions with alkynes. The resultant cycloadducts were in certain cases prone to two distinct rearrangement reactions based on their substitution at their C6-position to form pyrazoles and pyrazolotriazinones. These initial rearrangements spurred our research into rearrangement reactions of verdazyl derived cycloadducts into second generation heterocycles. A number of conditions can facilitate a heterocycle rearrangement. In chapter 6, heat promoted the rearrangement reactions observed. In other cases, as with the example in this chapter, an external nucleophile can cause a ring opening, initiating a rearrangement.¹

Alkene cycloadducts with acidic hydrogens were shown to rearrange under basic conditions as described in section 5.5 of this thesis. In an effort to further develop this rearrangement chemistry, especially towards biologically relevant compounds, a styrene-derived cycloadduct was exposed to acid-catalyzed hydrolytic conditions with the intent to force a ring opening. What would follow was open to speculation. Fortuitously, one major product was formed and identified as 3-methyl-5-phenyl-1,3,4-oxadiazolone. 1,3,4-Oxadiazolones have been shown to be important as ion channel inhibitors² and drugs for the treatment of malaria³ and tuberculosis⁴. This chapter outlines the acid catalyzed rearrangement of styrene derived cycloadducts with varying substituents at the C4-position showing the scope of the reaction to form 3-methyl-5-
aryl-1,3,4-oxadiazolones. A mechanism is proposed involving the incorporation of water and an isolated intermediate is provided as evidence for the mechanism.

7.2 Experimental

**Materials and Equipment:** All reagents and ACS grade solvents were purchased from Sigma-Aldrich or VWR unless otherwise stated. Column chromatography was performed with Silica Gel P60 (mesh size 40-63 µm) obtained from Silicycle. Thin layer chromatography (TLC) plates were obtained from EMD with Silica Gel 60 F254 and visualized under UV (254 nm) light. NMR spectra were recorded on a Bruker Avance III spectrometer at 23 °C, at 400 MHz for $^1$H NMR and 100 MHz for $^{13}$C NMR or on a Varian Unity INOVA-500 spectrometer at 23 °C, operating at 500 MHz for $^1$H NMR and 125 MHz for $^{13}$C NMR. Chemical shifts (δ) are reported in parts per million (ppm) referenced to tetramethylsilane (0 ppm) for $^1$H NMR spectra and CDCl$_3$ (77.0 ppm) for $^{13}$C NMR. Coupling constants (J) are reported in hertz (Hz). Spin multiplicities are indicated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Accurate mass determinations (HRMS) were carried out by the AIMS lab, Department of Chemistry, University of Toronto, using a Waters GC TOF mass spectrometer with an ESI source, MS/MS and accurate mass capabilities, associated with an Agilent 1100 capillary LC system. FT-IR spectra were acquired on a Nicolet Avatar 360 spectrometer using pellets prepared with KBr or as thin films on NaCl cells. Melting points were determined on an Electrothermal capillary melting point apparatus and are uncorrected. Single crystal X-ray structural determinations were carried out at the X-ray facility, Department of Chemistry, University of Toronto, on a Bruker-Nonius Kappa-CCD diffractometer using monochromated Mo-Kα radiation. Measurements were made using a combination of Φ and ω scans with κ offsets to fill the Ewald sphere. The data were processed using the Denzo-SMN
package. Absorption corrections were carried out using SORTAV. The structure was solved and refined using SHELXTL V6.1 for full-matrix least-squares refinement that was based on $F^2$. All hydrogen atoms were included in the calculated positions and allowed to refine in the riding-motion approximation with U-iso-tied to the carrier atom.

**General Cycloaddition Procedure:** 1,5-Dimethyl-3-phenyl-6-oxoverdazyl (203 mg, 1 mmol) was dissolved in 2 mL of THF in a 10 mL round bottom flask. Excess styrene (500 mg, 4.8 mmol) was added and the solution was refluxed for 24 hr. The reaction solution was cooled to ambient temperature and the unreacted styrene was removed *in vacuo*. The product was isolated by silica column chromatography (1:2 ethyl acetate/hexanes).

**General Hydrolysis Procedure:** The styrene cycloadduct (306 mg, 1 mmol) was dissolved in 5 mL of THF in a 25 mL round bottom flask equipped with a condenser. A 5 mL solution of 3 M HCl$_{aq}$ was added and the reaction was stirred and heated at 60 °C for 3 days. The reaction mixture was cooled to ambient temperature and extracted with 50 mL of dichloromethane 3 times. The dichloromethane extracts were combined, dried over sodium sulphate and evaporated to give an oil. The product was isolated by silica gel column chromatography (1:2 ethyl acetate/hexanes) and crystallized in 1:1 ethyl acetate/ hexanes.

2-Methyl-4,6-diphenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (7.1)
1,5-Dimethyl-3-phenyl-6-oxoverdazyl (203 mg) was reacted according to the general procedure for cycloaddition to yield a yellow waxy solid (257 mg, 84%); FT-IR (ν, cm$^{-1}$, KBr) 2929, 1675, 1607, 1363, 757, 696; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.44-7.40 (d, J = 7.2Hz, 2H), 7.35-7.30 (t, J = 7.2Hz, 1H), 7.27-7.20 (t, J = 8.0Hz, 2H), 7.18-7.12 (m, 3H), 6.93-6.88 (m, 2H), 4.74-4.69 (m, 1H), 4.39-4.30 (m, 1H), 3.67-3.58 (m, 1H), 3.20 (s, 3H), 2.61-2.50 (m, 1H), 2.26-2.14 (m, 1H); $^{13}$C NMR (100MHz, CDCl$_3$) δ 155.0 (C), 147.4 (C), 139.5 (C), 131.6 (C), 130.2 (CH), 128.2 (CH), 128.1 (CH), 127.8 (CH), 127.5 (CH), 127.2 (CH), 66.1 (CH$_3$), 44.8 (CH$_2$), 36.4 (CH), 33.3 (CH$_2$); HRMS (ESI): m/z [M]$^+$ calc’d for C$_{18}$H$_{19}$N$_4$O 307.15589, found 307.15632.

4-(4-Fluorophenyl)-2-methyl-6-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (7.2)

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1,5-Dimethyl-3-(4-fluoro)phenyl-6-oxoverdazyl (300 mg) was reacted according to the general procedure for cycloaddition to yield a yellow waxy solid (311 mg, 71%); FT-IR (ν, cm$^{-1}$, KBr) 3541, 3021, 2951, 1691, 1417, 1361; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.42-7.36 (m, 2H), 7.18-7.12 (m, 3H), 6.92-6.86 (m, 4H) 4.79-4.63 (m, 1H), 4.36-4.28 (m, 1H), 3.66-3.57 (m, 1H), 3.20 (s, 3H), 2.59-2.48 (m, 1H), 2.23-2.13 (m, 1H); $^{13}$C NMR (100MHz, CDCl$_3$) δ 164.9-162.4 (d, J = 249Hz) (C), 154.9 (C), 146.4 (C), 139.2 (C), 129.4-129.3 (d, J = 8.6Hz) (CH), 128.2 (CH), 127.8 (CH), 127.70-127.67 (d, J = 3Hz) (C), 127.1 (CH), 115.2-114.9 (d, J = 22Hz), 66.2 (CH), 44.8
CH+2, 36.3 (CH3), 33.3 (CH2); HRMS (ESI): m/z [M]+ calc’d for C18H17N4OF 324.1386, found 324.1390.

4-(4-Methoxyphenyl)-2-methyl-6-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (7.3)

1,5-Dimethyl-3-(4-methoxy)phenyl-6-oxoverdazyl (350 mg) was reacted according to the general procedure for cycloaddition to yield a yellow waxy solid (303 mg, 60%); FT-IR (ν, cm⁻¹, KBr) 2937, 1665, 1607, 1514, 1357, 1252, 1028; ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.33 (d, J = 8.8Hz, 2H), 7.18-7.14 (m, 3H), 6.93-6.88 (m, 4H) 6.78-6.73 (d, J = 8.8Hz, 2H), 4.72-4.67 (m, 1H), 3.39-3.31 (m, 1H), 3.79 (s, 3H), 3.64-3.56 (m, 1H), 3.18 (s, 3H), 2.60-2.50 (m, 1H), 2.25-2.15 (m, 1H); ¹³C NMR (100MHz, CDCl₃) δ 161.3 (C), 155.3 (C), 147.4 (C), 139.7 (C), 129.1 (CH), 128.3 (CH), 127.8 (CH), 127.3 (CH), 124.1 (C), 113.6 (CH), 66.2 (CH), 55.2 (CH₃), 44.9 (CH₂), 36.4 (CH₃), 33.4 (CH₂); HRMS (ESI): m/z [M]+ calc’d for C₁₉H₂₀N₄O₂ 336.1586, found 336.1577.

2-Methyl-6-phenyl-4-(3-(trifluoromethyl)phenyl)-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (7.4)
1,5-Dimethyl-3-(3-trifluoromethylphenyl)-6-oxovertazyl (700 mg) was reacted according to the general procedure for cycloaddition to yield a yellow waxy solid (612 mg, 63%); FT-IR (ν, cm⁻¹, KBr) 3554, 3478, 2949, 1681, 1617, 1321, 1127; ¹H NMR (400 MHz, CDCl₃) δ 7.63-7.62 (s, 1H), 7.61-7.58 (d, J = 8Hz, 1H), 7.54-7.50 (d, J = 8Hz, 1H) 7.35-7.29 (t, J = 8Hz, 1H), 7.16-7.09 (m, 3H), 6.91-6.87 (m, 2H), 4.67-4.62 (m, 1H), 4.32-4.24 (m, 1H), 3.75-3.67 (m, 1H), 3.25 (s, 3H), 2.61-2.51 (m, 1H), 2.25-2.14 (m, 1H); ¹³C NMR (100MHz, CDCl₃) δ 154.9 (C), 145.9 (C), 138.9 (C), 130.9-129.9 (q, J = 32.4Hz) (C), 130.4 (C), 128.5 (C), 128.3 (CH), 128.0 (C), 127.6-119.5 (q, J = 271Hz) (C), 127.2 (CH), 126.5-126.4 (q, J = 3.6Hz) (CH), 124.3-124.2 (q, J = 3.8Hz) (CH), 66.6 (CH₃), 45.0 (CH₂), 36.6 (CH), 33.4 (CH₂); HRMS (ESI): m/z [M+H]⁺ calc’d for C₁₉H₁₈N₄OF₃ 375.1427, found 375.1423.

2-Methyl-6-phenyl-4-(pyridin-2-yl)-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (7.5)
1,5-Dimethyl-3-(2-pyridylo)-6-oxoverdazyl (800 mg) was reacted according to the general procedure for cycloaddition to yield a yellow waxy solid (885 mg, 74%); FT-IR (v, cm⁻¹, KBr) 3550, 3472, 2946, 1669, 1408, 1194; ¹H NMR (400 MHz, CDCl₃) δ 8.59-8.56 (dq, J = 4.8Hz, 0.8Hz, 1H), 7.58-7.49 (dt, J = 8Hz, 1.6Hz, 1H), 7.48-7.44 (dt, J = 7.6Hz, 0.8Hz, 1H), 7.22-7.17 (ddd, J = 7.3Hz, 4.8Hz, 1.6Hz, 1H), 7.15-7.10 (m, 3H), 7.00-6.95 (m, 2H), 5.30-5.25 (m, 1H), 4.36-4.28 (m, 1H), 3.68-3.55 (m, 1H), 3.25 (s, 1H), 2.69-2.59 (m, 1H), 2.23-2.13 (m, 1H); ¹³C NMR (100MHz, CDCl₃) δ 155.0 (C), 149.9 (C), 148.7 (CH), 145.9 (C), 140.0 (C), 136.1 (CH), 128.2 (CH), 127.6 (CH), 126.8 (CH), 124.1 (CH), 122.4 (CH), 65.3 (CH₃), 44.3 (CH₂), 36.6 (CH), 33.7 (CH₂); HRMS (ESI): m/z [M]⁺ calc’d for C₁₇H₁₇N₅O 307.1433, found 307.1445.

4-(1H-Indol-6-yl)-2-methyl-6-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (7.6)

1,5-Dimethyl-3-(6-indole)-6-oxoverdazyl (100 mg) was reacted according to the general procedure for cycloaddition to yield off white crystals (68 mg, 48%); mp 160-162 °C; FT-IR (v, cm⁻¹, KBr) 3049, 3250, 2938, 1652, 1598, 1421, 1168; ¹H NMR (400 MHz, CDCl₃) δ 8.20-8.02 (br, 1H), 7.95-7.91 (d, J = 8Hz, 1H), 7.34-7.30 (d, J = 7.6Hz, 1H), 7.25-7.13 (m, 5H), 7.10-7.08 (d, J = 2.8Hz, 1H), 7.02-6.98 (m, 2H), 4.79-4.73 (m, 1H), 4.23-4.08 (m, 1H), 3.90-3.82 (m, 1H), 3.25 (s, 1H), 2.61-2.50 (m, 1H), 2.28-2.19 (m, 1H); ¹³C NMR
(100MHz, CDCl$_3$) $\delta$ 155.9 (C), 144.5 (C), 140.5 (C), 136.2 (C), 128.3 (CH), 127.8 (CH), 127.4 (CH), 126.8 (CH), 125.0 (C), 123.0 (CH), 121.3 (CH), 121.2 (CH), 111.1 (CH), 109.2 (C), 66.0 (CH), 45.1 (CH$^2$), 36.7 (CH$^3$), 33.4 (CH$^2$); HRMS (ESI): $m/z$ [M+H]$^+$ calc’d for C$_{20}$H$_{20}$N$_5$O 346.1662, found 346.1657.

4-(Furan-2-yl)-2-methyl-6-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (7.7)

![4-(Furan-2-yl)-2-methyl-6-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one](image)

1,5-Dimethyl-3-(2-furyl)-6-oxoverdazyl (600 mg) was reacted according to the general procedure for cycloaddition to yield a yellow waxy solid (256 mg, 65%); FT-IR (v, cm$^{-1}$, KBr) 3548, 3475, 2926, 1679, 1375, 1018; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36=7.34 (m, 1H), 7.25-7.18 (m, 3H), 7.09-7.05 (m, 2H) 6.45-6.42 (d, J = 3.2Hz, 1H), 6.29-6.26 (m, 1H), 4.90-4.84 (m, 1H), 4.20-4.10 (m, 1H), 3.72-3.62 (m, 1H), 3.21 (s, 3H), 2.60-2.48 (m, 1H), 2.22-2.11 (m, 1H);

$^{13}$C NMR (100MHz, CDCl$_3$) $\delta$ 155.4 (C), 144.6 (C), 143.8 (CH), 139.6 (C), 139.3 (C), 128.2 (CH), 127.7 (CH), 126.7 (CH), 112.6 (CH), 111.2 (CH), 65.7 (CH), 44.5 (CH$_2$), 36.3 (CH$_3$), 33.5 (CH$_2$); HRMS (ESI): $m/z$ [M+H]$^+$ calc’d for C$_{16}$H$_{17}$N$_4$O$_2$ 297.1346, found 297.1348.

2-Methyl-6-phenyl-4-(thiophen-3-yl)-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (7.8)
1,5-Dimethyl-3-(3-thiophene)-6-oxoverdazyl (100 mg) was reacted according to the general procedure for cycloaddition yield a yellow waxy solid (34.5 mg, 23%); FT-IR (ν, cm⁻¹, KBr)
3298, 3102, 2956, 1595, 1371, 1034; ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.33 (dd, J = 3.2Hz, 1.2Hz, 1H), 7.22-7.18 (m, 3H), 7.17-7.14 (dd, J = 4.8Hz, 3.0Hz, 1H), 7.06-7.03 (dd, J = 5.2Hz, 1.2Hz, 1H), 7.02-6.97 (m, 2H), 4.78-4.72 (m, 1H), 4.25-4.17 (m, 1H), 3.75-3.67 (m, 1H), 3.18 (s, 3H), 2.60-2.49 (m, 1H), 2.25-2.15 (m, 1H); ¹³C NMR (100MHz, CDCl₃) δ 155.1 (C), 143.8 (C), 139.8 (C), 133.8 (C), 128.4 (CH), 128.0 (CH), 127.3 (CH), 126.6 (CH), 126.3 (CH), 125.8 (CH), 66.4 (CH₃), 44.9 (CH₂), 36.5 (CH), 33.7 (CH₂); HRMS (ESI): m/z [M]^+ calc’d for C₁₆H₁₆N₄OS 312.1045, found 312.1043.

4,4’-(1,4-Phenylene)bis(2-methyl-6-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one) (7.9)
1,4-Bis-(1,5-dimethyl-6-oxoverdazyl)benzene (200 mg) was reacted according to the general procedure for cycloaddition to yield yellow crystals (107 mg, 33%); mp 194-197 °C; FT-IR (ν, cm\(^{-1}\), KBr) 3550, 2941, 1673, 1617, 1364; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.38-7.37 (s, 2H), 7.37-7.36 (s, 2H), 7.22-7.12 (m, 6H), 6.92-6.84 (m, 4H), 4.70-4.66 (m, 2H), 4.46-4.35 (m, 2H), 3.65-3.51 (m, 2H), 3.20-3.19 (s, 3H), 3.19-3.18 (s, 3H), 2.64-2.52 (m, 2H), 2.28-2.16 (m, 2H); \(^13\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 155.0 (C), 146.35 (C), 146.31 (C), 139.31 (C), 139.27 (C), 133.48 (C), 133.44 (C), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.32 (CH), 127.28 (CH), 127.25 (CH), 66.32 (CH\(_3\)), 66.25 (CH\(_3\)), 45.0 (CH\(_2\)), 36.6 (CH), 33.22 (CH\(_2\)), 33.18 (CH\(_2\)); HRMS (ESI): \(m/z\) [M+H]\(^+\) calc’d for C\(_{30}\)H\(_{31}\)N\(_8\)O\(_2\) 535.2564, found 535.2561.

3-Methyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one (7.10)

Compound 7.1 (306 mg) was reacted according to the general hydrolysis procedure to yield white crystals (129 mg, 73%); mp 64-65 °C; FT-IR (ν, cm\(^{-1}\), KBr) 3068, 1770, 1638, 1455, 1356, 1020; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.85-7.82 (m, 2H), 7.54-7.44 (m, 3H), 3.51 (s, 3H); \(^13\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 153.7 (C), 153.1 (C), 131.5 (CH), 128.9 (CH), 125.5 (CH), 123.8 (C), 32.7 (CH\(_3\)); HRMS (ESI): \(m/z\) [M+H]\(^+\) calc’d for C\(_9\)H\(_9\)N\(_2\)O 177.0658, found 177.0665.

5-(4-Fluorophenyl)-3-methyl-1,3,4-oxadiazol-2(3H)-one (7.11)
Compound 7.2 (311 mg) was reacted according to the general hydrolysis procedure to yield white crystals (119 mg, 64%); mp 86-88 °C; FT-IR (ν, cm⁻¹, KBr) 3537, 3086, 1782, 1611, 1508, 1225, 1015; ¹H NMR (400 MHz, CDCl₃) δ 7.84-7.80 (m, 2H), 7.18-7.13 (m, 2H), 3.50 (s, 3H); ¹³C NMR (100MHz, CDCl₃) δ 165.8 (C), 163.2 (C), 153.5-152.3 (d, J = 127Hz) (C), 127.8-127.7 (d, J = 8.8Hz) (CH), 120.1-120.0 (d, J = 3.2Hz) (C), 116.4-116.2 (d, J = 22.2Hz) (CH), 32.7 (CH₃); HRMS (ESI): m/z [M+H]⁺ calc’d for C₉H₈N₂O₂F 195.0564, found 195.0562.

5-(4-Methoxyphenyl)-3-methyl-1,3,4-oxadiazol-2(3H)-one (7.12)

Compound 7.3 (303 mg) was reacted according to the general hydrolysis procedure to yield white crystals (126 mg, 68%); mp 133-135 °C; FT-IR (ν, cm⁻¹, KBr) 2976, 2847, 1785, 1618, 1513, 1260, 1021; ¹H NMR (400 MHz, CDCl₃) δ 7.77-7.72 (d, J = 8.8Hz, 2H), 6.98-6.94 (d, J = 3.2Hz) (C), 116.4-116.2 (d, J = 22.2Hz) (CH), 32.7 (CH₃); HRMS (ESI): m/z [M+H]⁺ calc’d for C₉H₈N₂O₂F 195.0564, found 195.0562.
(C), 127.2 (CH), 116.1 (C), 114.3 (CH), 55.3 (CH₃), 32.5 (CH₃); HRMS (ESI): m/z [M+H]+ calc’d for C₁₀H₁₁N₂O₃ 207.0764, found 207.0767.

3-Methyl-5-(3-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2(3H)-one (7.13)

Compound 7.4 (600 mg) was reacted according to the general hydrolysis procedure to yield white crystals (310 mg, 79%); mp 38-39 °C; FT-IR (ν, cm⁻¹, KBr) 3555, 2950, 1782, 1612, 1577, 1180; ¹H NMR (400 MHz, CDCl₃) δ 8.09 (s, 1H), 8.01-7.97 (d, J = 8Hz, 1H) 7.78-7.74 (d, J = 8Hz, 1H), 7.65-7.59 (t, J = 8Hz, 1H) 3.53 (s, 3H); ¹³C NMR (100MHz, CDCl₃) δ 153.2 (C), 151.7 (C), 132.1-131.1 (q, J = 33Hz) (C), 129.6 (CH), 128.5 (CH), 127.9-127.8 (q, J = 3.6Hz) (CH), 124.7-119.3 (q, J = 271Hz) (C), 124.6 (C), 122.4-122.3 (q, J = 3.9Hz) (CH), 32.7 (CH₃); HRMS (ESI): m/z [M+H]+ calc’d for C₁₀H₈N₂O₂F₃ 245.0532, found 245.0543.

3-Methyl-5-(pyridin-2-yl)-1,3,4-oxadiazol-2(3H)-one (7.14)

Compound 7.5 (700 mg) was reacted according to the general hydrolysis procedure to yield white crystals (313 mg, 78%); mp 75-76 °C; FT-IR (ν, cm⁻¹, KBr) 3057, 1774, 1562, 1362, 1247,
5-(1H-Indol-6-yl)-3-methyl-1,3,4-oxadiazol-2(3H)-one (7.15)

Compound 7.6 (60 mg) was reacted according to the general hydrolysis procedure to yield a off white crystals (16 mg, 42%); mp 185-186 °C; FT-IR (ν, cm\(^{-1}\), KBr) 3551, 3252, 2942, 1764, 1633, 1449, 998; \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 8.80-8.60 (br, NH), 8.12-8.08 (d, J = 7.6Hz, 1H) 7.73-7.72 (d, J = 2.8Hz, 1H), 8.47-8.43 (d, J = 7.2Hz, 1H), 7.34-7.26 (m, 2H) 3.52 (s, 3H); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) δ 153.6 (C), 151.4 (C), 136.1 (C), 126.0 (CH), 123.8 (CH), 123.7 (C), 122.0 (CH), 121.0 (CH), 111.7 (CH), 101.8 (C), 32.7 (CH\(_3\)); HRMS (ESI): \(m/z\) [M+H]\(^+\) calc’d for C\(_{11}\)H\(_{10}\)N\(_3\)O\(_2\) 216.0778, found 216.0779.

5-(Furan-2-yl)-3-methyl-1,3,4-oxadiazol-2(3H)-one (7.16)
Compound 7.7 (256 mg) was reacted according to the general hydrolysis procedure to yield white crystals (11 mg, 8%); mp 91-93 °C; FT-IR (v, cm\(^{-1}\), KBr) 3138, 2924, 1779, 1645, 1471, 1225, 1016; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.60-7.58 (m, 1H), 6.98-6.96 (d, J = 3.6Hz, 2H), 6.57-6.55 (dd, J= 3.6Hz, 2Hz 1H) 3.50 (s, 3H); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 152.8 (C), 146.6 (C), 145.6 (CH), 138.9 (C), 113.5 (CH), 111.9 (CH), 32.9 (CH\(^3\)); HRMS (ESI): m/z [M+H]\(^+\) calc’d for C\(_7\)H\(_7\)N\(_2\)O\(_3\) 167.0451, found 167.0454.

3-Methyl-5-(thiophen-3-yl)-1,3,4-oxadiazol-2(3H)-one (7.17)

Compound 7.8 (34.5 mg) was reacted according to the general hydrolysis procedure to yield white crystals (9.2 mg, 46%); mp 68-70 °C; FT-IR (v, cm\(^{-1}\), KBr) 3475, 3131, 2922, 1774, 1619, 1310, 1107; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.86-7.84 (dd, J = 2.8Hz, 1.2Hz, 1H), 7.47-7.45 (dd, J = 5.2Hz, 1Hz) 7.44-7.41 (dd, J = 5.2Hz, 3.2Hz, 1H), 3.48 (s, 3H); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 153.4 (C), 150.4 (C), 127.5 (CH), 126.7 (CH), 125.3 (C), 124.6 (CH), 32.7 (CH\(^3\)); HRMS (ESI): m/z [M+H]\(^+\) calc’d for C\(_7\)H\(_7\)N\(_2\)S 183.0222, found 183.0221.
5,5’-(1,4-Phenylene)bis(3-methyl-1,3,4-oxadiazol-2(3H)-one) (7.18)

![Chemical structure of 5,5’-(1,4-Phenylene)bis(3-methyl-1,3,4-oxadiazol-2(3H)-one)](attachment:image)

Compound 7.9 (107 mg) was reacted according to the general hydrolysis procedure to yield white crystals (35 mg, 64%); mp 278-282 °C; FT-IR (ν, cm⁻¹, KBr) 3548, 3475, 1781, 1617, 1413, 1112; ¹H NMR (400 MHz, CDCl₃) δ 7.93 (s, 4H), 3.53 (s, 6H); ¹³C NMR (100MHz, CDCl₃) δ 153.4 (C), 152.1 (C), 126.3 (C), 126.1 (CH), 32.9 (CH₃); HRMS (ESI): m/z [M+H]+ calc’d for C₁₂H₁₁N₄O₄ 275.0774, found 275.0783.

N’-Benzoyl-N-methyl-3-phenylpyrazolidine-1-carbohydrazide (7.19)

![Chemical structure of N’-Benzoyl-N-methyl-3-phenylpyrazolidine-1-carbohydrazide](attachment:image)

Compound 7.1 (260 mg) was reacted according to the general hydrolysis procedure to yield a clear oil (19 mg, 7.7%); FT-IR (ν, cm⁻¹, KBr) 3191, 2958, 2872, 1729, 1689, 1620, 1289; ¹H NMR (400 MHz, CDCl₃) δ 9.36 (br, 1H), 7.90-7.84 (d, J = 7.6Hz, 2H), 7.54-7.48 (t, J = 7.2Hz, 1H), 7.33-7.38 (t, J = 8.0Hz, 2H), 7.32-7.22 (m, 5H), 5.00-4.30 (br, 1H), 4.20-4.14 (t, J = 7.6Hz, 1H), 3.84-3.76 (m, 1H), 3.66-3.56 (m, 1H), 3.25 (s, 3H), 2.48-2.37 (m, 1H), 2.14-2.00 (m, 1H); ¹³C NMR (100MHz, CDCl₃) δ 165.4 (C), 161.3 (C), 138.0 (C), 132.1 (C), 131.0 (C), 128.60 (CH), 128.57 (CH), 127.9 (CH), 127.3 (CH), 126.8 (CH), 63.0 (CH₃), 47.9 (CH₂), 38.3 (CH), 34.0 (CH₂); HRMS (ESI): m/z [M+H]+ calc’d for C₁₈H₂₁N₄O₂ 325.16645, found 325.16524.
4-Tert-butyl-2-methyl-6-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (7.20)

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\text{\includegraphics[width=0.3\textwidth]{structure1.png}}
\]

1,5-Dimethyl-3-(t-butyl)-6-oxoverdazyl (183 mg) was reacted according to the general procedure for cycloaddition to yield a yellow waxy solid (217.1 mg, 76%); FT-IR (\(\nu\), cm\(^{-1}\), KBr) 3173, 3142, 2988, 2954, 1595, 1351; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.33-7.27 (m, 2H), 7.25-7.19 (m, 3H), 4.92-4.86 (m, 1H), 4.10-4.02 (m, 1H), 3.38-3.28 (m, 1H), 3.12 (s, 3H), 2.56-2.45 (m, 1H), 2.07-1.96 (m, 1H), 1.05 (s, 9H); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 156.9 (C), 156.4 (C), 140.8 (C), 128.4 (CH), 127.6 (CH), 126.4 (CH), 65.6 (CH\(_3\)), 43.6 (CH\(_2\)), 36.3 (CH), 35.9 (C), 35.4 (CH\(_2\)), 28.7 (CH\(_3\)); HRMS (ESI): \(m/z\) [M]\(^+\) calc’d for C\(_{16}\)H\(_{23}\)N\(_4\)O 287.18719, found 287.18720.

4-Benzhydryl-2-methyl-6-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (7.22)

\[
\text{\includegraphics[width=0.3\textwidth]{structure2.png}}
\]

1,5-Dimethyl-3-(benzhydryl)-6-oxoverdazyl (110 mg) was reacted according to the general procedure for cycloaddition to yield yellow crystals (96 mg, 65%); mp 144-146 °C; FT-IR (\(\nu\), cm\(^{-1}\), KBr) 3025, 2901, 1684, 1619, 1493, 1384; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.44-7.25 (m,
10H), 7.15-7.06 (m, 3H), 6.80-6.74 (m, 2H), 4.57 (s, 1H), 4.44-4.37 (t, J = 7.2 Hz, 1H), 3.68-3.53 (m, 2H), 3.14 (s, 3H), 2.35-2.25 (m, 1H), 2.04-1.92 (m, 1H); $^{13}$C NMR (100MHz, CDCl$_3$) δ 157.1 (C), 151.5 (C), 140.6 (C), 139.6 (C), 138.6 (C), 129.07 (CH), 129.06 (CH), 128.81 (CH), 128.76 (CH), 128.2 (CH), 127.7 (CH), 127.3 (CH), 126.4 (CH), 126.1 (CH), 61.7 (CH$_3$), 51.8 (CH), 43.0 (CH$_2$), 36.3 (CH), 35.3 (CH$_2$); HRMS (ESI): m/z [M+H]$^+$ calc’d for C$_{25}$H$_{25}$N$_4$O 397.20284, found 397.20295.

2-Isopropyl-4,6-diphenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (7.24)

1-Isopropyl-5-methyl-3-phenyl-6-oxoverdazyl (110 mg) was reacted according to the general procedure for cycloaddition to yield a yellow waxy solid; FT-IR (v, cm$^{-1}$, KBr) 3062, 3030, 2973, 2933, 1719, 1671, 1450, 1384; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.65-7.59 (t, J = 7.2Hz, 1H), 7.50- 7.46 (m, 2H), 7.38-7.33 (t, J = 7.6Hz, 2H), 7.20-7.10 (m, 3H), 6.90-6.85 (d, J = 6.8Hz, 2H), 4.74-4.68 (m, 1H), 4.64-4.47 (m, 2H), 3.56-3.48 (m, 1H), 2.64-2.52 (m, 1H), 2.29-2.20 (m, 1H), 1.21-1.16 (d, J = 6.8Hz, 3H), 0.97-0.93 (d, J = 6.4Hz, 3H); $^{13}$C NMR (100MHz, CDCl$_3$) δ 154.2 (C), 146.5 (C), 139.3 (C), 133.0 (C), 130.0 (CH), 128.3 (CH), 128.1 (CH), 127.8 (CH), 127.5 (CH), 127.3 (CH), 66.0 (CH$_3$), 47.2 (CH$_2$), 44.8 (CH$_2$), 32.9 (CH$_2$), 19.8 (CH$_3$), 19.6 (CH$_3$); HRMS (ESI): m/z [M+H]$^+$ calc’d for C$_{25}$H$_{25}$N$_4$O 335.18719, found 335.18793.

3-Isopropyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one (7.25)
Compound **7.24** (25 mg) was reacted according to the general hydrolysis procedure to yield white crystals (9.2 mg, 61%); mp 45-47 °C; FT-IR (ν, cm\(^{-1}\), KBr) 2983, 2938, 2877, 1767, 1614, 1356; \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.88-7.87 (dd, J = 7.6 Hz, 1.2 Hz, 2H), 7.53-7.43 (m, 3H), 4.46-4.35 (sept, J = 6.8 Hz, 1H), 1.46-1.41 (d, J = 6.8 Hz, 6H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) δ 153.0 (C), 152.8 (C), 131.2 (CH), 128.7 (CH), 125.5 (CH), 124.0 (C), 48.1 (CH), 20.7 (CH);

HRMS (ESI): \[\text{m/z [M+H]}^+\] calc’d for C\(_{11}\)H\(_{13}\)N\(_2\)O\(_2\) 205.09770, found 205.09738.

**2-Benzyl-4,6-diphenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (7.26)**

1-Benzyl-5-methyl-3-phenyl-6-oxoverdazyl (110 mg) was reacted according to the general procedure for cycloaddition to yield yellow crystals; mp 99-101 °C; FT-IR (ν, cm\(^{-1}\), KBr) 3060, 3029, 2925, 1674, 1604, 1384; \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.37-7.35 (d, J = 7.2 Hz, 2H), 7.34-7.20 (m, 8H), 7.12-7.06 (t, J = 7.2 Hz, 1H), 7.01-7.94 (t, J = 8.0 Hz, 2H), 6.79-6.75 (d, J = 7.2 Hz, 2H), 4.98-4.92 (d, J = 14.8 Hz, 1H), 4.74-4.68 (m, 1H), 4.63-4.56 (d, J = 15.2 Hz, 1H) 4.49-4.42 (m, 1H), 3.59-3.53 (m, 1H), 2.62-2.51 (m, 1H), 2.23-2.12 (m, 1H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) δ 154.7 (C), 147.1 (C), 139.4 (C), 137.4 (C), 131.8 (C), 130.2 (CH), 128.25 (CH), 128.19 (CH), 128.17 (CH), 128.1 (CH), 127.7 (CH), 127.5 (CH), 127.1 (CH), 127.0 (CH), 66.3 (CH\(_3\)), 52.6
(CH₂), 44.8 (CH₂), 33.5 (CH₂); HRMS (ESI): m/z [M+H]^+ calc’d for C₂₄H₂₃N₄O 383.18719, found 383.18844.

3-Benzyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one (7.27)

![Chemical structure of 3-Benzyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one (7.27)]

Compound 7.26 (130 mg) was reacted according to the general hydrolysis procedure to yield a white solid (53.2 mg, 62%); mp 96-98 °C; FT-IR (ν, cm⁻¹, KBr) 3063, 3032, 2925, 2853, 1767, 1612, 1571; ^1H NMR (400 MHz, CDCl₃) δ 7.84-7.80 (dd, J = 8.0Hz, 1.2Hz, 2H), 7.51-7.30 (m, 8H), 4.95 (s, 2H); ^13C NMR (100MHz, CDCl₃) δ 153.4 (C), 153.2 (C), 134.8 (C), 131.4 (CH), 128.8 (CH), 128.7 (CH), 128.23 (CH), 128.17 (CH), 125.6 (CH), 123.7 (C), 49.6 (CH₂); HRMS (ESI): m/z [M+H]^+ calc’d for C₁₅H₁₃N₂O₂ 253.09770, found 253.09834.

7.3 Results and Discussion

With the goal of extending the scope of second generation compounds that can be made from verdazyl radical derived azomethine imine cycloadduct reactions, compound 7.1 was subjected to acidic hydrolysis conditions. As evidenced by TLC, heating 7.1 in a solution of 50:50 3M HCl(aq) : THF at 60 °C for 3 days led to the complete disappearance of starting material and the formation of one major product. Initially, the product was difficult to identify as it only contained a phenyl and methyl group in the ^1H NMR and the corresponding carbons, as well as, two additional quaternary carbons in the ^13C NMR; a simple spectrum for an unexpected compound. X-Ray crystallography was necessary to ascertain the identity of this major product which turned out to be 7.10, which formed in 73% yield.
Scheme 7-1. Oxadiazolone reaction scheme

The next step undertaken in this investigation was to generate a series of styrene cycloadducts with varying substituents at the C4-position and observe the scope and limitations of this rearrangement reaction. Cycloadduct products 7.2-7.9, 7.20, 7.22, 7.24 and 7.26 were synthesized and exposed to the rearrangement conditions. It was found that for cycloadducts with 4-aryl substitution, the rearrangement reaction proceeded well with yields ranging from 42% to 79% with the exception of 7.7 rearranging to 7.16 in only 8% yield. This exceptionally low yielding example can be explained by the furan group’s susceptibility to hydrolyze under the given reaction conditions hence leading to a breakdown of the final product 7.16. Results for these acid rearrangement reactions are summarized in Table 7-1.

<table>
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<th>Entry</th>
<th>Cycloadduct precursor</th>
<th>Product</th>
<th>Yield</th>
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<td><img src="image2.png" alt="Image" /></td>
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</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
<td>64%</td>
</tr>
<tr>
<td></td>
<td>Structure 1</td>
<td>Structure 2</td>
<td>Yield %</td>
</tr>
<tr>
<td>---</td>
<td>-------------</td>
<td>-------------</td>
<td>---------</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Structure 3.3" /></td>
<td><img src="image" alt="Structure 3.12" /></td>
<td>68%</td>
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<td><img src="image" alt="Structure 4.3" /></td>
<td><img src="image" alt="Structure 4.13" /></td>
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</tr>
<tr>
<td>5</td>
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<td><img src="image" alt="Structure 5.14" /></td>
<td>78%</td>
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</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Structure 7.3" /></td>
<td><img src="image" alt="Structure 7.16" /></td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td>46%</td>
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<td>-----</td>
</tr>
<tr>
<td>8</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
<td>7.8</td>
</tr>
<tr>
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<td><img src="image8.png" alt="Image" /></td>
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<td>7.25</td>
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Table 7-1. Alkene derived cycloadduct starting materials, 1,3,4-oxadiazolone acid hydrolysis products and reaction yields

The reaction conditions of 50:50 3M HCl\textsubscript{(aq)} : THF heating at 60 °C for 3 days were chosen as a balance between rate of reaction and mildness, however, to generate compounds 7.14, 7.24 and 7.26 higher temperatures (100 °C) were required to force the reaction to appreciable yields in 3 days. Cycloadducts with 4-alkyl substitution, namely 7.20 and 7.22, were expected to yield 7.21 and 7.23, respectively. Upon workup and chromatography, however, the alkyl substituted examples showed several unidentified decomposition products but no expected rearrangement products. A likely reason for this is that C=N double bond was not conjugated as with the 4-aryl examples leaving the LUMO too high and hence not electrophilic enough to be attacked efficiently by water to allow the rearrangement to proceed.
Scheme 7-2. Proposed mechanism for the rearrangement of verdazyl radical derived cycloadducts of styrene to form 1,3,4-oxadiazolones

A proposed mechanism for this transformation is shown in Scheme 7.2. The proposed mechanism starts with the N4 position being protonated under the strongly acidic conditions, forming an iminium ion, which is then attacked by water resulting in the opening of the tetrazinone ring. A series of proton exchanges results in compound 7.19, a small quantity of which (19 mg) was isolated, purified and characterized. When this isolated sample of 7.19 was exposed further to the same reaction acid reaction conditions, oxadiazolone 7.10 was formed as confirmed by TLC and $^1$H NMR. As proposed, compound 7.19 undergoes a 5-exo-trig ring closing reaction by attacking the carbonyl centre at C6, followed by a fragmentation reaction resulting in the final product. This fragmentation by-product, however, was not isolated.
Isolation by our methods may be difficult because the fragment may break down into volatile compounds upon workup or in the reaction mixture itself.

Before publishing these results in 2011, a literature search revealed compounds 7.14-7.18 had not previously reported. Given the biological relevance of this class of compounds as mentioned earlier it was somewhat peculiar that these simple heterocycle substituted examples had not been previously synthesized, implying perhaps a gap in current synthetic methodology. A commonly reported route to the synthesis of 3-methyl-5-aryl-1,3,4-oxadiazolones makes use of potassium salts of substituted hydrazides to attack phosgene to give 5-aryl substituted oxadiazolones, followed by N-methylation. Nucleophilic attack of acid chlorides with 1,1-dimethyl-2-substituted hydrazides provide another general route to these oxadiazolones. Lastly, oxadiazolones have been made via the rearrangement which occurs upon methylation of a precursor heterocycle 2-alkoxy substituted 1,3,4-oxadiazole. All of these methods rely on appropriately substituted hyrazides. Hydrazines have limited commercial availability based on substituents while verdazyl radicals provide the means to introduce a C5 substituted aryl group via an aldehyde. The next chapter of this thesis describes the hydrazine free synthesis of 6-oxoverdazyl radicals.

7.4 Summary
This project has demonstrated an extension to the synthetic usefulness of verdazyl radicals in synthesizing heterocyclic compounds of interest. 3-Methyl-5-aryl-1,3,4-oxadiazol-2(3H)-ones have been synthesized in yields ranging from 42% to 79% starting from verdazyl radical derived azomethine imine cycloadducts with styrene. A mechanism is proposed whereby the tetrazinone ring of these cycloadducts is open hydrolytically, followed by the incorporation of an oxygen atom from water. A fragmentation and ring closure afford the final product. Compound 7.19 was
isolated as a reaction intermediate to provide evidence for a mechanism proposed for this rearrangement.

7.5 References


8 Phosgene- and Hydrazine-Free Synthesis of 6-Oxoverdazyl Radicals

8.1 Introduction and Objective

Nearly all work in the Georges' lab in recent years has centered on using 6-oxoverdazyl radicals as substrates for organic synthesis. The method by which this 6-oxoverdazyl radical starting material was synthesized involved using Neugerbauer's\textsuperscript{1} methodology substituting phosgene with the relatively safer triphosgene\textsuperscript{2} as described in section 1.2. Reacting triphosgene with methyl hydrazine formed the dimethylhydrazide of carbonic acid, which when condensed with an aldehyde and oxidized led to the desired verdazyl radical starting materials. Recently, however, new US homeland security laws severely restricted the import of methyl hyrazine into Canada and with no domestic suppliers we were forced to undertake research into a new synthesis of verdazyl radicals. Fortunately this necessity led to the successful development of an alternative and much cheaper synthetic route with a wider scope than the previous employed method.

This chapter describes the development of a new synthetic method for generating 6-oxoverdazyl radicals. Unlike other syntheses, it is both free of triphosgene, as well as, hydrazine reagents. This method not only has allowed previously difficult to access alkyl substitutions on the N1 and N5 nitrogens but, because of selectivity in the alkylation process, has enabled the synthesis of unsymmetrically substituted verdazyl radicals. This new method has allowed the Georges lab to continue with verdazyl radical chemistry, as well as, make advances that would not have been possible with the limits of other synthetic methods.
8.2 Experimental

**Materials and Equipment:** All reagents and ACS grade solvents were purchased from Sigma-Aldrich or VWR unless otherwise stated. Column chromatography was performed with Silica Gel P60 (mesh size 40-63 µm) obtained from Silicycle. Thin layer chromatography (TLC) plates were obtained from EMD with Silica Gel 60 F$_{254}$ and visualized under UV (254 nm) light. NMR spectra were recorded on a Bruker Avance III spectrometer at 23 °C, at 400 MHz for $^1$H NMR and 100 MHz for $^{13}$C NMR or on a Varian Unity INOVA-500 spectrometer at 23 °C, operating at 500 MHz for $^1$H NMR and 125 MHz for $^{13}$C NMR. Chemical shifts (δ) are reported in parts per million (ppm) referenced to tetramethylsilane (0 ppm) for $^1$H NMR spectra and CDCl$_3$ (77.0 ppm) for $^{13}$C NMR. Coupling constants (J) are reported in hertz (Hz). Spin multiplicities are indicated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Accurate mass determinations (HRMS) were carried out by the AIMS lab, Department of Chemistry, University of Toronto, using a Waters GC TOF mass spectrometer with an ESI source, MS/MS and accurate mass capabilities, associated with an Agilent 1100 capillary LC system. FT-IR spectra were acquired on a Nicolet Avatar 360 spectrometer using pellets prepared with KBr or as thin films on NaCl cells. Melting points were determined on an Electrothermal capillary melting point apparatus and are uncorrected.

**Warning! Dimethyl sulfate (DMS) is considered carcinogenic, mutagenic and poisonous, use full lab safety equipment and caution when working with it.**

**General methanolysis and ring closure procedure:** Carbo-di(N'-benzylidene-N-methylhydrazide) (I) (5.00 g, 17 mmol) was dissolved in 250 mL of methanol. $p$-Toluenesulfonic acid (4.85 g, 25.5 mmol) and carbohydrazide (2.30 g, 25.5 mmol) were added to the solution and the reaction was allowed to stir for 1 hour at room temperature. Once the
reaction was complete, as indicated by disappearance of 1 on TLC, sodium methoxide was added incrementally until the solution was basic, pH ~ 10. Following this, the solvent was evaporated in vacuo and the crude product was filtered through a short silica gel column using 1:19 methanol in ethyl acetate as the eluent and recrystallized in 1:2 EtOAc in hexanes to yield white needle-like crystals (3.07 g, 88%): mp 103-105 °C; FT-IR (ν, cm⁻¹, KBr) 3254, 3218, 2967, 2938, 2877, 1598, 1506, 1451; ¹H NMR (400 MHz, CDCl₃) δ 7.55-7.51 (d, J = 7.3 Hz, 2H), 7.42-7.34 (m, 3H), 5.09-5.02 (t, J = 9.9 Hz, 1H), 4.40-4.35 (d, J = 10.0 Hz, 2H), 3.17 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 155.4, 135.2, 128.72, 128.67, 126.5, 69.4, 38.1; HRMS (ESI): m/z [M+H]⁺ calc’d for C₁₀H₁₅N₄O 207.12459, found 207.12373.

Carbo-di(N'-benzylidene-N-methylhydrazide) (8.1)

Carbo-di-N-benzylhydrazide (5.10 g, 19.1 mmol) was added to a 500 mL round bottom flask and dissolved in 200 mL of dry THF with stirring. Dimethylsulfate, 2.2 equivalents (5.30 g, 3.9 mL, 42.0 mmol) was added followed by a slow addition of 3 eq of sodium hydride (1.38 g, 57 mmol). The solution was brought to reflux and allowed to react for 2 hours. The reaction mixture was cooled to 0 °C and the unreacted sodium hydride was quenched by the slow addition of methanol until no effervescence was observed with added methanol. The solution volume was reduced in vacuo and the reaction mixture taken up in 100 mL of EtOAc and washed three times with 75 mL of water. The crude extract was dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo. The crude product was filtered through a short silica gel column (3:2
EtOAc in hexanes as the eluent) and recrystallized in 1:19 EtOAc in hexanes to yield off-white crystals (4.73 g, 85%) mp 131-134 °C; FT-IR (ν, cm⁻¹, KBr) 3062, 3030, 2952, 2919, 1656, 1597, 1478; ¹H NMR (400 MHz, CDCl₃) δ 7.74 (s, 2H), 7.66-7.60 (m, 4H), 7.32-7.27 (m, 6H), 3.49 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 158.4, 137.7, 135.3, 129.1, 128.6, 127.0, 32.9; HRMS (ESI): m/z [M+H]+ calc’d for C₁₇H₁₉N₄O 295.15589, found 295.15631.

**Carbo-di(N'-2-thienylidene-N-methylhydrazide) (8.2)**

Carbo-di-N-2-thienylhydrazide (1.00 g, 3.59 mmol) was added to a 100 mL round bottom flask and dissolved in 50 mL of dry THF with stirring. Dimethylsulfate, 2.2 eq, (1.22 g, 0.9 mL, 7.90 mmol) was added, followed by a slow addition of 3 eq of sodium hydride (259 mg, 10.8 mmol). The solution was heated at reflux for 2 hours. The reaction mixture was allowed to cool to 0 °C and the unreacted sodium hydride was carefully quenched with the slow addition of methanol. The solution volume was reduced in vacuo and the reaction mixture taken up in 50 mL of EtOAc and washed three times with 50 mL of water. The crude extract was dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo. The crude product was isolated using silica gel column chromatography (2:3 EtOAc in hexanes as the eluent) and recrystallized in 1:4 EtOAc in hexanes to yield white crystals (613 mg, 56%): mp 160-163 °C; FT-IR (ν, cm⁻¹, KBr) 3086, 3072, 1645, 1587, 1420; ¹H NMR (400 MHz, CDCl₃) δ 7.90 (s, 2H), 7.24-7.19 (m, 4H), 7.02-6.99 (m, 2H), 3.43 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 157.6, 140.6, 132.8, 127.9,
126.9, 126.7, 33.1; HRMS (ESI): $m/z$ [M+H]$^+$ calc’d for C$_{13}$H$_{15}$N$_4$O$_2$ 307.06873, found 307.06962.

**Carbo-di(N'-benzylidene-N-benzylhydrazide) (8.3)**

![Chemical Structure](image)

Carbo-di-N-benzylhydrazide (6.00 g, 22.5 mmol) was added to a 500 mL round bottom flask and dissolved in 150 mL of anhydrous toluene with stirring. Benzylbromide, 2.2 eq, (8.40 g, 5.9 mL, 49.6 mmol) was added followed by the slow addition of 3 eq of sodium hydride (1.62 g, 67.6 mmol). The solution heated at reflux for 24 hours. The reaction mixture was allowed to cool to 0 °C and the unreacted sodium hydride was carefully quenched by the slow addition of methanol. The solution was taken up in 100 mL of EtOAc and washed three times with 70 mL of water. The crude extract was dried over anhydrous sodium sulfate and the solvent was evaporated *in vacuo*. The resulting product was filtered through a short silica gel column (DCM as the eluent) and recrystallized in methanol to yield colourless granular crystals (9.16 g, 91%). mp 117-120 °C; FT-IR (ν, cm$^{-1}$, KBr) 3052, 2972, 2927, 1669, 1602, 1495; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.64 (s, 2H), 7.43-7.38 (m, 8H), 7.37-7.32 (m, 4H), 7.29-7.22 (m, 3H), 7.21-7.14 (m, 5H), 5.36 (s, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 158.9, 139.1, 135.9, 134.9, 128.9, 128.7, 128.3, 127.0, 126.9, 126.3, 49.3; HRMS (ESI): $m/z$ [M+H]$^+$ calc’d for C$_{39}$H$_{27}$N$_4$O 447.21849, found 447.21949.

**Carbo-di(N'-benzylidene-N-ethylhydrazide) (8.4)**
Carbo-di-N-benzylhydrazide (7.00 g, 26.3 mmol) was added to a 500 mL round bottom flask and dissolved in 150 mL of anhydrous toluene with stirring. Diethylsulfate, 2.2 eq, (8.90 g, 7.4 mL, 57.9 mmol) was added followed by a slow addition of 3 eq of sodium hydride (1.89 g, 78.9 mmol). The solution was brought to reflux and allowed to react for 24 hours. The reaction mixture was allowed to cool to 0 °C and the unreacted sodium hydride was quenched by the slow addition of methanol. The solution was then taken up in 100 mL of EtOAc and washed three times with 75 mL of water. The crude extract was dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo. The crude product was filtered through a short silica gel column (1:199 methanol in DCM as the eluent) and recrystallized from 1:19 EtOAc in hexanes to yield off-white crystals (6.95 g, 82%): mp 83-85 °C; FT-IR (ν, cm⁻¹, KBr) 3022, 2978, 2934, 2873, 1659, 1604, 1597, 1464; ¹H NMR (400 MHz, CDCl₃) δ 7.81 (s, 2H), 7.61-7.56 (m, 4H), 7.28-7.24 (m, 6H), 4.10-4.03 (q, J = 7.1 Hz, 4H), 1.34-1.28 (t, J = 7.1 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 157.8, 138.5, 135.2, 128.9, 128.4, 126.8, 39.8, 11.2; HRMS (ESI): m/z [M+H]^+ calc’d for C₁₉H₂₃N₄O 323.18719, found 323.18744.

Carbo-N'-benzylidene(N'-benzylidene-N-benzylhydrazide) (8.5)
Carbo-di-N-benzylhydrazide (5.00 g, 18.8 mmol) was added to a 500 mL round bottom flask and dissolved in 250 mL of dried THF with stirring. Benzylbromide, 1.1 eq, (3.53 g, 2.46 mL, 20.7 mmol) was added followed by the slow addition of 2 eq of sodium hydride (901 mg, 37.6 mmol). The solution was heated to reflux and allowed to react for 4 hours. The reaction mixture was allowed to cool to 0 °C and the unreacted sodium hydride was quenched by the slow addition of methanol. This solution was then taken up in 150 mL of EtOAc and washed three times with 100 mL of water. The crude extract was dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo. The crude product was filtered through a short silica gel column (1:49 methanol in DCM as the eluent) and recrystallized from 1:9 EtOAc in hexanes to yield off-white crystals (5.35 g, 80%): mp 188-191 °C; FT-IR (ν, cm⁻¹, KBr) 3338, 3029, 1708, 1607, 1498, 1485; ¹H NMR (400 MHz, CDCl₃) δ 10.02 (s, 1H), 8.15 (s, 1H), 7.82-7.77 (m, 2H), 7.58-7.51 (m, 3H), 7.42-7.21 (m, 11H), 5.30 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 152.4, 145.5, 138.8, 135.1, 133.9, 129.8, 129.7, 128.8, 128.6, 128.5, 127.33, 127.29, 126.8, 126.5, 45.3; HRMS (ESI): m/z [M+H]⁺ calc’d for C₂₂H₂₁N₄O 357.17154, found 357.17284.

Carbo-N'-benzylidene-N-benzylhydrazide(N'-benzylidene-N-methylhydrazide) (8.6)

Carbo-N'-benzylidene-N-benzylhydrazide(N'-benzylidene-N-methylhydrazide) (8.5) (2.40 g, 6.73 mmol) was added to a 250 mL round bottom flask and dissolved in 100 mL of anhydrous toluene with stirring. Dimethylsulfate, 1.1 eq, (934 mg, 0.70 mL, 7.40 mmol) was added followed by slow a addition of 2 eq of sodium hydride (323 mg, 13.5 mmol). The solution was heated to 85 °C and allowed
to react for 2 hours. The reaction mixture was allowed to cool to 0 °C and the unreacted sodium hydride was quenched by the slow addition of methanol. The solution volume was reduced in vacuo. This solution was then taken up in 75 mL of EtOAc and washed three times with 50 mL of water. The crude extract was dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo. The crude product was filtered through a short silica gel column (DCM as the eluent) and recrystallized from methanol to yield off-white crystals (2.20 g, 88%): mp 97-99 °C; FT-IR (v, cm⁻¹, KBr) 3061, 3024, 1708, 1667, 1604, 1423; ¹H NMR (400 MHz, CDCl₃) δ 7.76 (s, 1H), 7.62 (s, 1H), 7.54-7.46 (m, 4H), 7.39-7.30 (m, 4H), 7.28-7.17 (m, 7H), 5.30 (s, 2H), 3.53 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 158.5, 139.1, 137.7, 135.9, 135.1, 134.9, 128.93, 128.90, 128.7, 128.4, 128.3, 127.0, 126.89, 126.86, 126.3, 49.3, 32.7; HRMS (ESI): m/z [M+H]+ calc’d for C₂₃H₂₃N₄O 371.18719, found 371.18559.

**Carbo-N'-benzylidene-N-benzylhydrazide(N'-benzylidene-N-ethylhydrazide) (8.7)**

![Chemical structure]

Carbo-N'-benzylidene(N'-benzylidene-N-benzylhydrazide) (8.5) (625 mg, 1.75 mmol) was added to a 100 mL round bottom flask and dissolved in 20 mL of anhydrous toluene with stirring. Diethylsulfate, 1.2 eq, (324 mg, 0.27 mL, 2.10 mmol) was added followed by a slow addition of 2 eq of sodium hydride (84 mg, 3.51 mmol). The solution was heated to reflux and allowed to react for 10 hours. The reaction mixture was allowed to cool to 0 °C and the unreacted sodium hydride was quenched by a slow addition of methanol and the solution volume was reduced in vacuo. This solution was then taken up in 50 mL of EtOAc and washed once with 100 mL 1M
NaOH\textsubscript{(aq)} and two more times with 100 mL of water. The crude extract was dried over anhydrous sodium sulfate and the solvent was evaporated \textit{in vacuo}. The crude product was filtered through a short silica gel column (DCM as the eluent) to yield an orange oil (510 mg, 75%): FT-IR (\nu, cm\textsuperscript{-1}, KBr) 3061, 3025, 2974, 2933, 1665, 1598, 1426; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \delta 7.81 (s, 1H), 7.61 (s, 1H), 7.50-7.42 (m, 4H), 7.39-7.29 (m, 4H), 7.27-7.13 (m, 7H), 5.28 (s, 2H), 4.16-4.04 (q, J = 6.9 Hz, 2H), 1.36-1.29 (t, J = 6.8 Hz, 3H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \delta 158.3, 139.1, 138.6, 136.2, 135.2, 135.1, 129.0, 128.9, 128.8, 128.5, 128.3, 127.05, 126.94, 126.93, 126.4, 49.6, 39.7, 11.2; HRMS (ESI): m/z [M+H]\textsuperscript{+} calc’d for C\textsubscript{24}H\textsubscript{25}N\textsubscript{4}O 385.20284, found 385.20202.

\textbf{Carbo-N'-benzylidene-N-benzylhydrazide(N'-benzylidene-N-ethylhydrazide) (8.8)}

\[ \text{Carbo-di-N-benzylhydrazide (5.00 g, 18.8 mmol) was added to a 500 mL round bottom flask and dissolved in 250 mL of dried THF with stirring. Diethylsulfate, 1.1 eq, (3.18 g, 2.6 mL, 20.7 mmol) was added followed by a slow addition of 2 eq of sodium hydride (902 mg, 37.6 mmol). The solution was heated to reflux and allowed to react for 4 hours. The reaction mixture was allowed to cool to 0 °C and the unreacted sodium hydride was quenched by the slow addition of methanol. The solution was then taken up in 150 mL of EtOAc and washed three times with 75 mL of water. The crude extract was dried over anhydrous sodium sulfate and the solvent was evaporated \textit{in vacuo}. The crude product was filtered through a short silica gel column (1:99 methanol in DCM as the eluent) and recrystallized from 1:9 EtOAc in hexanes to yield off-white} \]
crystals (4.38 g, 79%): mp 128-130 °C; FT-IR (ν, cm⁻¹, KBr) 3298, 3267, 3018, 2979, 1681, 1516, 1404; ¹H NMR (400 MHz, CDCl₃) δ 9.85 (s, 1H), 8.07 (s, 1H), 7.78-7.74 (m, 2H), 7.68-7.64 (m, 3H), 7.46-7.33 (m, 6H), 4.13-4.07 (q, J = 7.1 Hz, 2H), 1.24-1.19 (t, J = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 151.7, 145.1, 137.0, 134.3, 134.0, 129.63, 129.61, 128.7, 128.4, 127.2, 126.7, 35.4, 11.0; HRMS (ESI): m/z [M+H]+ calc’d for C₁₈H₂₁N₄O 309.17154, found 309.17177.

**Carbo-N'-benzylidene-N-ethylhydrazide(N'-benzylidene-N-methylhydrazide) (8.9)**

![Chemical structure](image)

Carbo-N'-benzylidene-N-benzylhydrazide(N'-benzylidene-N-ethylhydrazide) (8.8) (4.37 g, 14.8 mmol) was added to a 500 mL round bottom flask and dissolved in 200 mL of anhydrous toluene with stirring. Dimethylsulfate, 1.2 eq, (2.24 g, 1.7 mL, 17.8 mmol) was added followed by a slow addition of 2 eq of sodium hydride (710 mg, 29.6 mmol). The solution was heated to 85 °C and allowed to react for 2 hours. The reaction mixture was allowed to cool to 0 °C and the unreacted sodium hydride was quenched by the slow addition of methanol and the solution volume was reduced *in vacuo*. The solution was then taken up in 150 mL of EtOAc and washed three times with 100 mL of water. The crude extract was dried over anhydrous sodium sulfate and the solvent was evaporated *in vacuo*. The crude product was filtered through a short silica gel column (1:199 methanol in DCM as the eluent) to yield off white crystals (4.02 g, 88%): mp 99-101 °C; FT-IR (ν, cm⁻¹, KBr) 3062, 3023, 2980, 2933, 2903, 1651, 1598, 1427; ¹H NMR (400 MHz, CDCl₃) δ 7.80 (s, 1H), 7.73 (s, 1H), 7.64-7.58 (m, 4H), 7.31-7.25 (m, 6H), 4.12-4.04 (q, J
\[ \text{132} \]

\[ 7.1 \text{ Hz}, 2\text{H}), 3.47 \text{ (s, 3H), 1.34-1.29 (t, J = 7.0 \text{ Hz, 3H); }^{13}\text{C NMR (100MHz, CDCl}_3\delta 158.0, 138.5, 137.3, 135.2, 135.1, 129.0, 128.8, 128.41, 128.36, 126.9, 126.8, 39.6, 33.0, 11.1; HRMS (ESI): } m/z \text{ [M+H]}^+ \text{ calc’d for C}_{18}\text{H}_{21}\text{N}_4\text{O 309.17154, found 309.17245.} \]

**Carbo-N’-benzylidene-N-methylhydrazide(N’-benzylidene-N-propylhydrazide) (8.10)**

![Chemical Structure](image)

Carbo-N’-benzylidene(N’-benzylidene-N-propylhydrazide) (8.11) (2.00 g, 6.49 mmol) was added to a 250 mL round bottom flask and dissolved in 40 mL of anhydrous toluene with stirring. Dimethylsulfate, 1.4 eq, (1.15 g, 0.86 mL, 9.08 mmol) was added followed by a slow addition of 2.2 eq of sodium hydride (340 mg, 14.3 mmol). The solution was heated to 85 °C and allowed to react for 2 hours. The reaction mixture was allowed to cool to 0 °C and the unreacted sodium hydride was quenched by the slow addition of methanol and the solution volume was reduced in vacuo. This solution was then taken up in 75 mL of EtOAc and washed three times with 50 mL of water. The crude extract was dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo. The crude product was filtered through a short silica gel column (1:99 methanol in DCM as the eluent) to yield a light yellow oil (1.67 g, 80%): FT-IR (\( \nu \text{, cm}^{-1} \), KBr) 3059, 3027, 2962, 2932, 2874, 1666, 1598, 1572, 1422; \(^1\text{H NMR (400 MHz, CDCl}_3\delta 7.74 \text{ (s, 1H), 7.65 \text{ (s, 1H), 7.63-7.56 (m, 4H), 7.24-7.17 (m, 6H), 4.98-4.91 (t, J = 7.4 \text{ Hz, 2H), 3.37 (s, 3H), 1.79-1.68 (sextet, J = 7.4 \text{ Hz, 2H), 1.00-0.93 (t, J = 7.4 \text{ Hz, 3H); }^{13}\text{C NMR (100 MHz, CDCl}_3\delta 158.2, 138.3, 137.3, 135.3, 135.2, 129.0, 128.8, 128.42, 128.37, 126.89, 126.85, 46.3, 33.0, 19.2, 11.2; HRMS (ESI): } m/z \text{ [M+H]}^+ \text{ calc’d for C}_{19}\text{H}_{23}\text{N}_4\text{O 323.1866, found 323.1866.} \]

Carbo-N'-benzylidene(N'-benzylidene-N-propylhydrazide) (8.11)

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Carbo-di-N-benzylhydrazide (2.50 g, 9.39 mmol) was added to a 500 mL round bottom flask and dissolved in 100 mL of dried THF with stirring. Iodopropane, 1.2 eq, (1.92 g, 1.1 mL, 11.3 mmol) was added followed by a slow addition of 2 eq of sodium hydride (451 mg, 18.8 mmol). The solution was heated to reflux and allowed to react for 24 hours. The reaction mixture was allowed to cool to 0 °C and the unreacted sodium hydride was quenched by the slow addition of methanol. This solution was then taken up in 100 mL of EtOAc and washed three times with 75 mL of water. The crude extract was dried over anhydrous sodium sulfate and the solvent was evaporated \textit{in vacuo}. The crude product was filtered through a short silica gel column (2:98 methanol in DCM as the eluent) and recrystallized from 1:9 EtOAc in hexanes to yield off-white crystals (2.14 g, 74%): mp 114-116 °C; FT-IR (ν, cm\(^{-1}\), KBr) 3327, 2960, 2937, 2874, 1695, 1608, 1511, 1402; \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 9.88 (s, 1H), 8.05 (s, 1H), 7.77-7.73 (m, 2H), 7.67-7.63 (m, 2H), 7.61 (s, 1H), 7.45-7.31 (m, 6H), 4.02-3.96 (t, J = 7.5 Hz, 2H), 1.70-1.59 (sextet, J = 7.5 Hz, 2H), 1.00-0.95 (t, J = 7.4 Hz, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) δ 152.1, 145.1, 137.1, 134.2, 134.0, 129.6, 128.7, 128.4, 127.2, 126.7, 42.1, 18.9, 11.0; HRMS (ESI): \(m/z\) [M+H]\(^+\) calc’d for C\(_{18}\)H\(_{21}\)N\(_4\)O 309.17154, found 309.17177.

\textit{2,4-Dimethyl-6-phenyl-1,2,4,5-tetrazinan-3-one} (8.12)
Carbo-di(N'-benzylidene-N-methylhydrazide) (8.1) (5.00 g) was reacted according to the general methanolysis and ring closure procedure to yield white needle-like crystals (3.07 g, 88%): mp 103-105 °C; FT-IR (ν, cm⁻¹, KBr) 3254, 3218, 2967, 2938, 2877, 1598, 1506, 1451; ¹H NMR (400 MHz, CDCl₃) δ 7.55-7.51 (d, J = 7.3 Hz, 2H), 7.42-7.34 (m, 3H), 5.09-5.02 (t, J = 9.9 Hz, 1H), 4.40-4.35 (d, J = 10.0 Hz, 2H), 3.17 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 155.4, 135.2, 128.72, 128.67, 126.5, 69.4, 38.1; HRMS (ESI): m/z [M+H]⁺ calc’d for C₁₀H₁₅N₄O 207.12459, found 207.12373.

**2,4-Dimethyl-6-(thiophen-2-yl)-1,2,4,5-tetrazinan-3-one (8.13)**

Carbo-di(N'-2-thienylidene-N-methylhydrazide) (8.2) (193 mg) was reacted according to the general methanolysis and ring closure procedure to yield white needle-like crystals (82 mg, 62%): mp 123-125 °C; FT-IR (ν, cm⁻¹, KBr) 3246, 2970, 2923, 2875, 1602, 1507, 1434; ¹H NMR (400 MHz, CDCl₃) δ 7.32-7.29 (d, J = 4.9 Hz, 1H), 7.16-7.13 (m, 1H), 7.04-7.00 (t, J = 4.5 Hz, 1H), 5.24-5.18 (t, J = 8.8 Hz, 1H), 4.58-4.53 (d, J = 8.8 Hz, 2H), 3.15 (s, 6H); ¹³C NMR.
(100MHz, CDCl$_3$) $\delta$ 155.1, 138.1, 127.1, 126.0, 125.8, 66.9, 38.1; HRMS (ESI): $m/z$ [M+H]$^+$ calc’d for C$_8$H$_{13}$N$_4$OS 213.08101, found 213.08115.

2,4-Dibenzyl-6-phenyl-1,2,4,5-tetrazinan-3-one (8.14)

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\text{N} \text{N} \text{NH}
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Carbo-di(N'-benzylidene-N-benzylhydrazide) (8.3) (1.50 g) was reacted according to the general methanolysis and ring closure procedure to yield white needle-like crystals (1.09 g, 91%): mp 147-150 °C; FT-IR (v, cm$^{-1}$, KBr) 3256, 3249, 3227, 1594, 1501, 1449; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.45-7.24 (m, 15H), 4.82-4.67 (m, 5H), 4.23-4.17 (d, J = 10.8 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 154.0, 137.6, 134.8, 128.6, 128.4, 128.3, 127.3, 126.1, 69.5, 53.1; HRMS (ESI): $m/z$ [M+H]$^+$ calc’d for C$_{22}$H$_{23}$N$_4$O 359.18719, found 359.18893.

2,4-Diethyl-6-phenyl-1,2,4,5-tetrazinan-3-one (8.15)

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\text{N} \text{N} \text{NH}
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Carbo-di(N'-benzylidene-N-ethylhydrazide) (8.4) (347 mg) was reacted according to the general methanolysis and ring closure procedure to yield white needle-like crystals (252 mg, 82%): mp 70-72 °C; FT-IR (v, cm$^{-1}$, KBr) 3231, 3063, 3034, 2972, 2930, 2868, 1600, 1496, 1452, 1421; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.56-7.52 (m, 2H), 7.43-7.34 (m, 3H), 4.94-4.86 (t, J = 11.2 Hz, 1H),
4.19-4.13 (d, J = 11.3 Hz, 2H), 3.73-3.63 (sextet, J = 7.0 Hz, 2H), 3.56-3.45 (sextet, J = 7.0 Hz, 2H), 1.23-1.18 (t, J = 7.0 Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 154.4, 135.4, 128.8, 128.7, 126.3, 70.4, 44.6, 12.4; HRMS (ESI): m/z [M+H]$^+$ calc’d for C$_{12}$H$_{19}$N$_4$O 235.15589, found 235.15581.

2-Benzyl-4-methyl-6-phenyl-1,2,4,5-tetrazinan-3-one (8.16)

![Chemical Structure of 2-Benzyl-4-methyl-6-phenyl-1,2,4,5-tetrazinan-3-one](image)

Carbo-N'-benzylidene-N-benzylhydrazide(N'-benzylidene-N-methylhydrazide) (8.6) (6.10 g) was reacted according to the general methanolysis and ring closure procedure to yield white needle-like crystals (2.11 g, 45%): mp 98-100 °C; FT-IR (v, cm$^{-1}$, KBr) 3238, 3030, 2909, 1687, 1597, 1514; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.48-7.27 (m, 10H), 4.99-4.92 (t, J = 10.4 Hz, 1H), 4.79-4.73 (d, J = 14.5 Hz, 1H), 4.69-4.63 (d, J = 14.5 Hz, 1H), 4.35-4.30 (d, J = 10.4 Hz, 1H), 4.24-4.19 (d, J = 10.3 Hz, 1H), 3.21 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 154.4, 137.7, 134.9, 128.62, 128.57, 128.5, 128.3, 127.2, 126.2, 69.4, 53.5, 37.9; HRMS (ESI): m/z [M+H]$^+$ calc’d for C$_{16}$H$_{19}$N$_4$O 283.15589, found 283.15616.

2-Benzyl-4-ethyl-6-phenyl-1,2,4,5-tetrazinan-3-one (8.17)

![Chemical Structure of 2-Benzyl-4-ethyl-6-phenyl-1,2,4,5-tetrazinan-3-one](image)
Carbo-N'-benzylidene-N-benzylhydrazide(N'-benzylidene-N-ethylhydrazide) (8.7) (290 mg) was reacted according to the general methanolysis and ring closure procedure to yield an orange oil (154 mg, 69%); FT-IR (ν, cm⁻¹, KBr) 3234, 3062, 3030, 2971, 2927, 1613, 1495, 1451; ¹H NMR (400 MHz, CDCl₃) δ 7.46-7.20 (m, 10H), 4.82-4.56 (m, 3H), 4.35-4.27 (m, 2H), 3.73-3.62 (sextet, J = 7.0 Hz, 1H), 3.46-3.36 (sextet, J = 7.0 Hz, 1H), 1.19-1.14 (d, J = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 154.0, 137.8, 135.1, 128.5, 128.4, 128.3, 127.2, 126.2, 69.8, 53.5, 44.6, 12.3; HRMS (ESI): m/z [M+H]⁺ calc’d for C₁₇H₂₁N₄O 297.17154, found 297.17162.

2-Ethyl-4-methyl-6-phenyl-1,2,4,5-tetrazinan-3-one (8.18)

Carbo-N'-benzylidene-N-ethylhydrazide(N'-benzylidene-N-methylhydrazide) (8.9) (200 mg) was reacted according to the general methanolysis and ring closure procedure to yield white needle-like crystals (70 mg, 49%) mp 78-80 °C; FT-IR (ν, cm⁻¹, KBr) 3251, 3226, 2972, 2932, 2871, 1593, 1490, 1450, 1430; ¹H NMR (400 MHz, CDCl₃) δ 7.54-7.48 (m, 2H), 7.40-7.28 (m, 3H), 4.89-4.81 (t, J = 10.0 Hz, 1H), 4.78-4.72 (d, J = 10.0 Hz, 1H), 4.64-4.58 (d, J = 10.0 Hz, 1H), 3.75-3.55 (sextet, J = 7.0 Hz, 1H), 3.41-3.30 (sextet, J = 7.0 Hz, 1H), 3.10 (s, 3H), 1.18-1.10 (t, J = 6.9 Hz, 3H); ¹³C NMR (100MHz, CDCl₃) δ 154.6, 135.3, 128.4, 128.3, 127.2, 126.2, 69.7, 44.5, 37.8, 12.4; HRMS (ESI): m/z [M+H]⁺ calc’d for C₁₁H₁₇N₄O 221.14024, found 221.13961.

2-Methyl-6-phenyl-4-propyl-1,2,4,5-tetrazinan-3-one (8.19)
Carbo-N’-benzylidene-N-methylhydrazide(N’-benzylidene-N-propylhydrazide) (8.10) (500 mg) was reacted according to the general methanolysis and ring closure procedure to yield a yellow-orange oil (262 mg, 72%); FT-IR (ν, cm⁻¹, KBr) 3235, 3061, 3032, 2961, 2930, 2873, 1690, 1616, 1451; ¹H NMR (400 MHz, CDCl₃) δ 7.54-7.48 (m, 2H), 7.40-7.28 (m, 3H), 4.92-4.84 (t, J = 9.9 Hz, 1H), 4.77-4.69 (d, J = 10.1 Hz, 1H), 4.62-4.54 (d, J = 9.9 Hz, 1H), 3.55-3.44 (m, 1H), 3.37-3.26 (m, 1H), 3.11 (s, 3H), 1.68-1.55 (sextet, J = 7.3 Hz, 2H) 0.93-0.84 (t, J = 7.3 Hz, 3H); ¹³C NMR (100MHz, CDCl₃) δ 154.8, 135.5, 128.6, 126.5, 69.7, 51.6, 38.0, 20.7, 11.3; HRMS (ESI): m/z [M+H]+ calc’d for C₁₂H₁₉N₄O 235.1553, 235.1558 found.

**Methyl N’,2-dibenzylidene-1-methylhydrazinecarbohydrazonothioate (8.20)**

Thiocarbo-di-N-benzylhydrazide (1.00 g, 3.54 mmol) was added to a 250 mL round bottom flask and dissolved in 75 mL of dried THF with stirring. Dimethylsulfate, 2.2 eq, (0.98 g, 0.7 mL, 7.79 mmol) was added followed by a slow addition of 3 eq of sodium hydride (254 mg, 10.6 mmol). The solution was brought to reflux and allowed to react for 2 hours. The reaction mixture was allowed to cool to 0 °C, the unreacted sodium hydride was quenched by the slow addition of methanol and the solution volume was reduced *in vacuo*. This solution was then taken up in 50
mL of EtOAc and washed three times with 100 mL of water. The extract was dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo. The crude product was recrystallized from 1:9 EtOAc in hexanes to yield bright yellow crystals (1.03 g, 94%): mp 64-65 °C; FT-IR (ν, cm⁻¹, KBr) 3055, 3020, 2925, 1593, 1567, 1510, 1406; ¹H NMR (400 MHz, CDCl₃) δ 8.30 (s, 1H), 7.79-7.73 (m, 2H), 7.70-7.65 (d, J = 7.3 Hz, 2H), 7.62 (s, 1H), 7.42-7.34 (m, 5H), 7.34-7.28 (t, J = 7.2 Hz, 1H), 3.55 (s, 3H), 2.63 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 164.0, 155.7, 136.3, 135.3, 135.1, 129.9, 128.8, 128.6, 128.5, 127.7, 126.6, 33.4, 17.8; HRMS (ESI): m/z [M+H]⁺ calc’d for C₁₇H₁₉N₄S 311.13304, found 311.13254.

**Carbo-N’-benzylidene(N’-benzylidene-N-allylhydrazide) (8.21)**

![Chemical Structure](image)

Carbo-di-N-benzylhydrazide (2.80 g, 10.5 mmol) was added to a 250 mL round bottom flask and dissolved in 100 mL of dried THF with stirring. Allylbromide, 5 eq, (6.36 g, 4.5 mL, 52.5 mmol) was added followed by a slow addition of 2 eq of sodium hydride (876 mg, 21.0 mmol). The solution was heated to reflux and allowed to react for 24 hours. The reaction mixture was allowed to cool to 0 °C and the unreacted sodium hydride was quenched by the slow addition of methanol. This solution was then taken up in 100 mL of EtOAc and washed three times with 200 mL of water. The extract was dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo. The crude product was filtered through a short silica gel column (1:49 methanol in DCM as the eluent) and recrystallized from 1:9 EtOAc in hexanes to yield yellow crystals (1.80 g, 56%): mp 43-45 °C; FT-IR (ν, cm⁻¹, KBr) 3347.1, 3060.6, 3024.6, 1678.5,
1510.4, 1486.3; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.95 (s, 1H), 8.08 (s, 1H), 7.78-7.73 (m, 2H), 7.66-7.62 (m, 2H), 7.58 (s, 1H), 7.44-7.32 (m, 6H), 5.84-5.73 (m, 1H), 5.22-5.12 (m, 2H), 4.69-4.65 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 151.9, 145.4, 138.7, 134.1, 134.0, 130.5, 129.71, 129.69, 128.7, 128.4, 127.2, 126.8, 117.0, 43.5; HRMS (ESI): $m/z$ [M+H]$^+$ calc’d for C$_{18}$H$_{19}$N$_4$O 307.1553, found 307.1558.

**Carbo-N'-benzylidene-N-methylhydrazide(N'-benzylidene-N-allylhydrazide) (8.22)**

![Carbo-N'-benzylidene-N-methylhydrazide(N'-benzylidene-N-allylhydrazide)](image)

Carbo-N'-benzylidene(N'-benzylidene-N-allylhydrazide) (8.11) (1.30 g, 4.24 mmol) was added to a 100 mL round bottom flask and dissolved in 50 mL of anhydrous THF with stirring. Dimethylsulfate, 1.2 eq, (643 mg, 0.48 mL, 5.10 mmol) was added followed by a slow addition of 2 eq of sodium hydride (204 mg, 8.48 mmol). The solution was heated to reflux and allowed to react for 3 hours. The reaction mixture was allowed to cool to 0 °C and the unreacted sodium hydride was quenched by the slow addition of methanol and the solution volume was reduced *in vacuo*. This solution was then taken up in 75 mL of EtOAc and washed three times with 75 mL of water. The crude extract was dried over anhydrous sodium sulfate and the solvent was evaporated *in vacuo*. The crude product was filtered through a short silica gel column (1:99 methanol in DCM eluent) to yield a light orange oil (1.17 g, 86%): FT-IR ($\nu$, cm$^{-1}$, KBr) 3060.1, 3024.1, 1664.3, 1606.0, 1421.5, 1384.4; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.67 (s, 1H), 7.64 (s, 1H), 7.63-7.55 (m, 4H), 7.22-7.16 (m, 6H), 5.92-5.80 (m, 1H), 5.34-5.26 (d, $J$ = 17.3 Hz, 1H), 5.22-5.16 (d, $J$ = 10.6 Hz, 1H), 4.64-4.60 (m, 2H), 3.37 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$
HRMS (ESI): m/z [M+H]+ calcd for C_{19}H_{21}N_{4}O 321.1709, found 321.1710.

2-Methyl-6-phenyl-4-allyl-1,2,4,5-tetrazinan-3-one (8.23)

2-Methyl-6-phenyl-4-allyl-1,2,4,5-tetrazinan-3-one (8.23)

Carbo-N'-benzylidene-N-methylhydrazide(N'-benzylidene-N-allylhydrazide) (8.22) (1.04 g, 4.48 mmol) was reacted according to the general methanolysis and ring closure procedure to yield white crystals (632 mg, 84%); mp: 74-76 °C; FT-IR (ν, cm\(^{-1}\), KBr) 3250.3, 3226.1, 3084.0, 3009.3, 2971.4, 2910.4, 1696.4, 1488.8; \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.52-7.48 (m, 2H), 7.37-7.27 (m, 3H), 5.89-5.77 (m, 1H), 5.25-5.18 (dd, \(J = 17.1\) Hz, 1.5 Hz, 1H), 5.16-5.11 (dd, \(J = 10.2\) Hz, 1.3 Hz, 1H), 4.92-4.80 (m, 2H), 4.77-4.70 (d, \(J = 8.9\)Hz, 1H), 4.14-4.06 (m, 1H), 3.93 (m, 1H), 3.09 (s, 3H); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) δ 154.4, 135.3, 133.5, 128.4, 126.5, 117.1, 69.5, 52.6, 37.8; HRMS (ESI): m/z [M+H]+ calcd for C_{12}H_{17}N_{4}O 233.1396, 233.1395 found.

Carbo-di-(N'-3-phenylpropionyl-N-methylhydrazide) (8.24)
Carbo-di-N-3-phenylpropionylhydrazide (815 mg, 2.52 mmol) was added to a 100 mL round bottom flask and dissolved in 50 mL of dried THF with stirring. Dimethylsulfate, 2.2 eq, (732 mg, 0.55 mL, 5.79 mmol) was added followed by a slow addition of 3 eq of sodium hydride (0.182 g, 7.58 mmol). The solution was brought to reflux and allowed to react for 2 hours. The reaction mixture was allowed to cool to 0 °C and the unreacted sodium hydride was quenched by the slow addition of methanol and the solution volume was reduced in vacuo. This solution was then taken up in 100 mL of EtOAc and washed three times with 75 mL of water. The crude extract was dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo. The crude product was filtered through a short silica gel column (1:1 EtOAc in hexanes as the eluent) to yield a yellow oil (0.797 g, 90%); FT-IR (ν, cm⁻¹, KBr) 3060, 3025, 2926, 1623, 1479, 1453, 1385, 1334; ¹H NMR (400 MHz, CDCl₃) δ 7.30-7.26 (m, 4H), 7.22-7.17 (m, 6H), 7.03 (t, 2H), 3.18 (s, 6H), 2.86 (t, 4H), 2.65 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 158.8, 141.1, 140.9, 128.5, 128.4, 126.1, 34.5, 33.4, 33.1; HRMS (ESI): m/z [M+H]+ calc’d for C₂₁H₂₇N₄O 351.21849, found 351.21844.

2,4-Dimethyl-6-(3-phenyl)propionyl-1,2,4,5-tetrazinan-3-one (8.25)

Carbo-di(N'-3-phenylpropionyl-N-methylhydrazide) (8.24) (0.424 g) was reacted according to the general methanolysis and ring closure procedure to yield an off white solid (130 g, 46%); mp 82-84 °C; FT-IR (ν, cm⁻¹, KBr) 3232, 3205, 2956, 2919, 2869, 1597, 1495, 1439, 1392; ¹H NMR
(400 MHz, CDCl₃) δ 7.32-7.26 (m, 2H), 7.23-7.17 (m, 3H), 4.21-4.12 (d, J = 9.9 Hz, 2H), 3.82-3.69 (m, 1H), 3.07 (s, 6H), 2.81-2.74 (m, 2H), 1.82 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 155.3, 140.7, 128.36, 128.31, 126.0, 67.0, 37.9, 31.7, 31.6.1; HRMS (ESI): m/z [M+H]^+ calc’d for C₁₀H₁₅N₄O 207.12459, found 207.12373.

Carbo-di(N’-paravinylicbenzylidene-N-ethylhydrazide) (8.26)

Carbo-di-N-paravinylicbenzylhydrazide (1.21 g, 4.53 mmol) was added to a 100 mL round bottom flask and dissolved in 50 mL of anhydrous toluene with stirring. Diethylsulfate, 4 eq, (2.79 g, 2.3 mL, 18.1 mmol) was added followed by a slow addition of 6 eq of sodium hydride (0.651 g, 27.1 mmol). The solution was brought to reflux and allowed to react for 39 hours. The reaction mixture was allowed to cool to 0 °C and the unreacted sodium hydride was quenched by a slow addition of methanol. The solution was then taken up in 100 mL of EtOAc and washed three times with 75 mL of water. The crude extract was dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo. The crude product was filtered through a short silica gel column (1:1 EtOAc in hexanes as the eluent) and recrystallized from 1:19 EtOAc in hexanes to yield off-yellow solids (396 mg, 28%): mp 78-81 °C; FT-IR (ν, cm⁻¹, KBr) 3025, 2933, 1666, 1624, 1453, 1385, 1086, 752, 700; ¹H NMR (400 MHz, CDCl₃) δ 7.78 (s, 2H), 7.58-7.28 (m, 8H), 6.72-6.61 (dd, J = 10.9 Hz, 6.9 Hz, 2H), 5.76-5.67 (d, J = 17.8 Hz, 2H), 5.27-5.20 (d, J =
11.8 Hz, 2H), 4.09-4.01 (q, J = 6.9 Hz, 4H), 1.34-1.27 (t, J = 7.0 Hz, 6H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 157.9, 138.3, 138.2, 136.4, 134.9, 127.1, 126.4, 114.3, 39.9, 11.3; HRMS (ESI): \(m/z\) [M+H]\textsuperscript{+} calc’d for C\textsubscript{23}H\textsubscript{27}N\textsubscript{4}O 375.21849, found 375.21848.

\textbf{2,4-Diethyl-6-paravinylphenyl-1,2,4,5-tetrazinan-3-one (8.27)}

\begin{center}
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\draw (1,0) -- (2,1) -- (3,0) -- (2,-1) -- cycle;
\draw (2,0) -- (3,1) -- (4,0) -- (3,-1) -- cycle;
\draw (3,0) -- (4,1) -- (5,0) -- (4,-1) -- cycle;
\end{tikzpicture}
\end{center}

Carbo-di(N'-paravinylicbenzylidene-N-ethylhydrazide) (8.26) (108 mg) was reacted according to the general methanolysis and ring closure procedure to yield yellow oil (48 mg, 64%): FT-IR (\(\nu\), cm\textsuperscript{-1}, KBr) 3233, 2968, 2930, 1609, 1428, 1261, 1126, 1080, 1016; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.53-7.48 (m, 2H), 7.45-7.40 (m, 2H), 6.77-6.67 (dd, J = 6.8 Hz, 10.9 Hz, 1H), 5.82-5.74 (d, J = 17.8 Hz, 1H), 5.33-5.26 (d, J = 10.9 Hz, 1H), 4.94-4.85 (t, J = 11.2 Hz, 1H), 4.20-4.11 (d, J = 11.3 Hz, 2H), 3.74-3.62 (sextet, J = 7.0 Hz, 2H), 1.24-1.16 (t, J = 7.0 Hz, 6H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 154.4, 138.2, 136.1, 134.6, 126.4, 114.8, 70.1, 44.6, 12.4; HRMS (ESI): \(m/z\) [M+H]\textsuperscript{+} calc’d for C\textsubscript{14}H\textsubscript{21}N\textsubscript{4}O 261.17154, found 261.17221.
8.3 Results and Discussion

An alternative synthesis to making 6-oxoverdazyl radicals is accomplished without the use of phosgene (or triphosgene) or hydrazines. Due to the NMR incompatible nature of verdazyl radicals, the synthesis of their tetrazinanone precursors is given in order to facilitate the full characterization of previously unreported compounds. Generating the final verdazyl radicals from their respective tetrazinanone precursors is a trivial matter of oxidation widely described in literature using any one of a number of oxidants, such as NaIO₄, K₃Fe(CN)₆, PbO₂ or Dess-Martin reagent, to afford the verdazyl radicals.³

![Scheme 8-1: Synthetic pathway](image_url)

This new synthesis allows for the variable substitution of positions N1, C3 and N5 in the final 6-oxoverdazyl radical represented as R³, R¹ and R², respectively, in 8.31 (Scheme 8-1). The common starting material used is carbohydrazide, 8.28, a cheap and safe to handle reagent. Condensing carbohydrazide with an aldehyde serves to protect the -NH₂ groups from alkylation in the following step, as well as, introduce the R¹ substituent. With the -NH₂ groups protected, alkylation can proceed on the α-nitrogens of 8.29 without chemoselectivity issues. It was found that dialkylsulfates work best for alkylation since their higher boiling points allowed for heating to higher temperatures, for example refluxing toluene, in cases where alkylation was proceeding at an unsatisfactory rate. For dialkylations, 2.2 eq. of alkylation agent was used. Interestingly, it
was observed that the second alkylation occurred slower than the first. By limiting the alkylating agent to 1.1 eq., mono-alkylation was accomplished for several examples. Alkylating the other side with a different alkyl group allowed for unsymmetrically substituted (R² and R³) examples of 8.30.

The last step to generate the tetrazinanones necessitated cleavage of one of the hydrazone groups on 8.30 to allow intramolecular cyclization to close the 6-membered ring. Originally, acidic aqueous hydrolysis conditions were used but this led to low yields of tetrazinanone. This could be partly attributed to difficulties associated with the variable solubility of tetrazinanones in water and ethyl acetate during extraction. Eventually, methanol was used instead of water in the reaction and an acid catalyzed “methanolysis” reaction generated the tetrazinanone, however, yields were still unsatisfactory. It was discovered, by following the reaction by TLC and ¹H NMR, that the conversion of 8.30 to the tetrazinanone 8.31 stopped at approximately 50% and these two compounds then remained in equilibrium with each other under the acidic reaction conditions. An aldehyde trap was necessary to perturb this equilibrium and drive the reaction forward. Carbohydrazide 8.28 was devised as the ideal trap having two sites to condense with aldehydes. The mono- and di-hydrazone trap products precipitated out of solution and were filtered off. These trap products could in theory be recycled back into the first step.

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<th>Product of second alkylation</th>
<th>% Yield of second alkylation</th>
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Table 8-1: Products and reaction yields of mono- and di-alkylation and methanolysis/ ring closure reactions of tetrazinanone syntheses.

A series of tetrazinanones prepared by this method to show of the scope of the synthetic procedure is summarized in table 8-1. Most alkylations proceeded in high yield (28-91%), however, this method is only conducive to introducing primary alkyl groups. Alkylations with secondary alkyl iodides (isopropyl iodide and cyclohexyl iodide) were attempted, however, they did not lead to any alkylated material. Thiocarbohydrazide was used in place of carbohydrazide in an attempt to extend this methodology to 6-thioverdazyl radicals, however, alkylation was observed to occur selectively on the sulfur and only one of the target nitrogen sites affording

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compound **8.20** exclusively in 94% yield rather than the target di-N-alkylated product. The yields of the methanolysis and ring closure reactions ranged from 45-91%. This to date is the only method used to generate unsymmetrically substituted 1,5-dialkyl-6-oxoverdazyl radicals. As discussed in section 1.3 of this thesis, Milcent et al.\(^5\) showed a synthesis for 1,5-unsymmetrical 6-oxoverdazyl radicals with two different aryl substituents. Brook et al.\(^6\) capitalized on this to produce the unsymmetrical 1-isopropyl-3,5-di-(2-pyridyl)-6-oxoverdazyl radical in their studies of verdazyl metal complexes. The synthetic scheme they devised still makes use of phosgene and hydrazines but can be used complementarily to overcome the shortfall of not being able to introduce secondary alkyl groups using the method described herein.

### 8.4 Summary

In conclusion, a complementary synthesis to current methodologies for the synthesis of 6-oxoverdazyl radicals is described. This method does not rely on the use of phosgene or hydrazines that have limited commercial availability and limit the number of possible substituents for the N1 and N5 positions of 6-oxoverdazyl radicals. By using a stepwise alkylation procedure, this method allows unsymmetrical substitution patterns in 1,5-dialkyl-6-oxoverdazyl radicals that have not been previously reported in literature. However, alkyl substituents are limited to primary alkyl examples. An initial condensation reaction of carbohydrazide with an aldehyde protects the NH\(_2\) groups during the subsequent N1 and N5 alkylation reactions and introduces the desired C3 substituent in the final verdazyl radical product. A subsequent methanolysis and concomitant ring closing reaction affords the tetrazinanone. A number of known oxidation methods can then be used to make the final verdazyl radical product.
8.5 References


Chapter 9

9 Unsymmetrical Verdazyl Radicals: Their Reactivity towards Dipolarophiles

9.1 Introduction and Objective

With the development of a new 1,5-dialkyl-6-oxoverdazyl radical synthesis described in chapter 8 of this thesis, the possibility of a wider range of alkyl substitution patterns in these verdazyl radicals has been realized. The ability to generate 1,5-dialkyl-6-oxoverdazyl radicals with various alkyl groups capable of undergoing a disproportionation reaction to generate previous unreported azomethine imines provides the opportunity to expand the chemistry so far developed by the Georges lab. In addition, it provides the ability to generate unsymmetrically N1 and N5 substituted verdazyl radicals.

It was initially assumed that a methyl group would always be more reactive to the disproportionation reaction, in comparison to other alkyls groups (ethyl, propyl, etc.), because of its smaller size. Generally, radicals having substituents with greater steric bulk are more stable. With this in mind, we anticipated that in the case where the verdazyl radical had two sites for disproportionation, a methyl and a larger alkyl group, the azomethine imine would predominately, if not exclusively, form on the more accessible methyl side leading to predictable cycloaddition reaction products (Scheme 9-1).
Scheme 9-1. Azomethine imines predicted to form preferentially on the methyl side of an unsymmetrical substituted verdazyl radical.

Upon synthesizing unsymmetrical verdazyl radicals and exposing them to our cycloaddition reaction conditions we were surprised to observe that in fact the bulkier groups were the major contributors in generating the azomethine imine dipoles based on the product distributions of the cycloadducts. This seemed to go against conventional wisdom regarding the stabilizing effects of sterically bulky substituents stabilizing radicals. This chapter outlines a series of cycloaddition reactions derived from unsymmetrical verdazyl radicals and includes an attempt to rationalize the results.

9.2 Experimental

Materials and Equipment: All reagents and ACS grade solvents were purchased from Sigma-Aldrich or VWR unless otherwise stated. Column chromatography was performed with Silica Gel P60 (mesh size 40-63 μm) obtained from Silicycle. Thin layer chromatography (TLC) plates were obtained from EMD with Silica Gel 60 F254 and visualized under UV (254 nm) light. NMR spectra were recorded on a Bruker Avance III spectrometer at 23 °C, at 400 MHz for $^1$H NMR and 100 MHz for $^{13}$C NMR. Chemical shifts (δ) are reported in parts per million (ppm) referenced to tetramethylsilane (0 ppm) for $^1$H NMR spectra and CDCl$_3$ (77.0 ppm) for $^{13}$C NMR. Coupling constants (J) are reported in hertz (Hz). Spin multiplicities are indicated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br
(broad). Accurate mass determinations (HRMS) were carried out by the AIMS lab, Department of Chemistry, University of Toronto, using a Waters GC TOF mass spectrometer with an ESI source, MS/MS and accurate mass capabilities, associated with an Agilent 1100 capillary LC system. FT-IR spectra were acquired on a Nicolet Avatar 360 spectrometer using pellets prepared with KBr or as thin films on NaCl cells. Melting points were determined on an Electrothermal capillary melting point apparatus and are uncorrected. Verdazyl radicals were synthesized according to published procedures.\(^1,2\)

**General Cycloaddition Reaction Procedure:** 1-Ethyl-5-methyl-3-phenyl-6-oxoverdazyl (217 mg, 1.00 mmol) was dissolved in 2 mL of THF in a 10 mL round bottom flask. Excess methyl acrylate (0.817 mL, 10.0 mmol) was added and the solution was refluxed for 24 hr. The reaction solution was cooled to ambient temperature and the unreacted methyl acrylate was removed *in vacuo*. The product was isolated by silica column chromatography (1:2 ethyl acetate/hexanes) and recrystallized in 1:1 ethyl acetate/hexanes.

**Methyl 2,8-dimethyl-1-oxo-4-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazine-6-carboxylate (9.1)**

![Chemical Structure](image)

1-Ethyl-5-methyl-3-phenyl-6-oxoverdazyl (217 mg, 1.00 mmol) was reacted according to the general procedure for the cycloaddition reaction to yield yellow crystals mp 58-60 °C (193 mg, 64%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.64-7.60 (d, \(J = 7.7\) Hz, 2H), 7.47-7.36 (m, 3H), 4.65-4.55 (sextet, \(J = 6.9\) Hz, 1H), 4.29-4.25 (dd, \(J = 8.4\) Hz, 2.8 Hz, 1H), 3.61 (s, 3H), 3.34 (s, 3H), 2.49-
Methyl 2-ethyl-1-oxo-4-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazine-6-carboxylate (9.2)

\[
\begin{align*}
\text{Ph} & \quad \text{CO}_2\text{Me} \\
N \quad \quad N \\
\quad \quad \quad \quad \quad \quad X
\end{align*}
\]

1-Ethyl-5-methyl-3-phenyl-6-oxoverdazyl (217 mg, 1.00 mmol) was reacted according to the general procedure for the cycloaddition reaction to yield a yellow oil (33.2 mg, 11%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.67-7.63 (d, \(J = 7.8\) Hz, 2H), 7.47-7.36 (m, 3H), 4.26-4.18 (m, 2H), 3.88-3.78 (m, 1H), 3.78-3.69 (m, 1H), 3.55 (s, 3H), 3.51-3.43 (m, 1H), 2.47-2.37 (m, 1H), 2.29-2.20 (m, 1H), 1.32-1.26 (t, \(J = 7.1\) Hz, 3H); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 171.1, 153.6, 145.8, 131.1, 130.7, 128.5, 127.5, 62.0, 52.2, 44.0, 43.8, 29.6, 13.1; HRMS (ESI): \(m/z\) [M+H]\(^+\) calc’d for C\(_{15}\)H\(_{19}\)N\(_4\)O\(_3\) 303.14571, found 303.14561.

Methyl 1-oxo-4-phenyl-2-propyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazine-6-carboxylate (9.3)

\[
\begin{align*}
\text{Ph} & \quad \text{CO}_2\text{Me} \\
N \quad \quad N \\
\quad \quad \quad \quad \quad \quad X
\end{align*}
\]

Methyl 1-oxo-4-phenyl-2-propyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazine-6-carboxylate (9.3)
5-Methyl-3-phenyl-1-propyl-6-oxoverdazyl (231 mg, 1.00 mmol) was reacted according to the general procedure for the cycloaddition reaction to yield yellow crystals mp 41-43 °C (41.6 mg, 13%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.66-7.62 (d, J = 7.6 Hz, 2H), 7.47-7.36 (m, 3H), 4.25-4.18 (m, 2H), 3.79-3.70 (m, 1H), 3.66-3.57 (m, 1H), 3.55 (s, 3H), 3.52-3.44 (m, 1H), 2.47-2.37 (m, 1H), 2.28-2.19 (m, 1H), 1.81-1.71 (sextet, J = 7.5 Hz, 2H), 1.01-0.95 (t, J = 7.4 Hz, 3H); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 171.1, 153.8, 145.6, 131.1, 130.6, 128.5, 127.5, 62.0 52.2, 50.5, 44.0, 29.6, 21.3, 10.9; HRMS (ESI): m/z [M+H]\(^+\) calc’d for C\(_{16}\)H\(_{21}\)N\(_4\)O\(_3\) 317.16136, found 317.16153.

Methyl 8-ethyl-2-methyl-1-oxo-4-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazine-6-carboxylate (9.4)

![Chemical Structure](image)

Methyl 2-benzyl-1-oxo-4-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazine-6-carboxylate (9.4)

5-Methyl-3-phenyl-1-propyl-6-oxoverdazyl (231 mg, 1.00 mmol) was reacted according to the general procedure for the cycloaddition reaction to yield yellow crystals mp 41-43 °C (41.6 mg, 13%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.65-7.61 (d, J = 7.7 Hz, 2H), 7.47-7.36 (m, 3H), 4.48-4.40 (quintet, J = 7.0 Hz, 1H), 4.27-4.23 (dd, J = 8.7 Hz, 2.7 Hz, 1H), 3.61 (s, 3H), 3.35 (s, 3H), 2.47-2.39 (m, 1H), 2.21-2.12 (m, 1H), 1.82-1.70 (m, 1H), 1.66-1.54 (m, 1H), 1.03-0.99 (t, J = 7.4 Hz, 3H); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 171.1, 153.8, 145.6, 131.1, 130.6, 128.5, 127.5, 62.0 52.2, 50.5, 44.0, 35.1, 28.0, 10.5; HRMS (ESI): m/z [M+H]\(^+\) calc’d for C\(_{16}\)H\(_{21}\)N\(_4\)O\(_3\) 317.16136, found 317.16271.

Methyl 2-benzyl-1-oxo-4-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazine-6-carboxylate (9.5)
1-Benzyl-5-methyl-3-phenyl-6-oxoverdazyl (265 mg, 1.00 mmol) was reacted according to the general procedure for the cycloaddition reaction to yield off white crystals mp 103-105 °C (65.5 mg, 18%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.61-7.57 (d, J = 7.7 Hz, 2H), 7.49-7.45 (d, J = 7.4 Hz, 2H), 7.45-7.30 (m, 6H), 5.00-4.95 (d, J = 14.9 Hz, 1H), 4.82-4.76 (d, J = 14.9 Hz, 1H), 4.28-4.20 (m, 2H), 3.52-3.44 (m, 1H), 2.47-2.37 (m, 1H), 2.30-2.21 (m, 1H), 2.28-2.19 (m, 1H); $^{13}$C NMR (100MHz, CDCl$_3$) $\delta$ 171.0, 153.8, 145.6, 137.6, 130.9, 130.7, 128.5, 128.2, 127.5, 127.1, 62.1, 52.6, 52.0, 44.0, 29.5; HRMS (ESI): $m/z$ [M+H]$^+$ calc’d for C$_{20}$H$_{21}$N$_4$O$_3$ 365.16136, found 365.15991.

Methyl 2-methyl-1-oxo-4,8-diphenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazine-6-carboxylate (9.6)

1-Benzyl-5-methyl-3-phenyl-6-oxoverdazyl (265 mg, 1.00 mmol) was reacted according to the general procedure for the cycloaddition reaction to yield off white crystals mp 128-129 °C (182 mg, 50%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.67-7.63 (d, J = 7.8 Hz, 2H), 7.47-7.34 (m, 7H), 7.30-7.25 (m, 1H), 5.66-5.61 (m, 1H), 4.36-4.32 (dd, J = 8.3 Hz, 3.0 Hz, 1H), 3.64 (s, 3H), 3.37 (s, 3H), 2.83-2.75 (m, 1H), 2.59-2.51 (m, 1H); $^{13}$C NMR (100MHz, CDCl$_3$) $\delta$ 170.8, 153.9, 145.4,
141.1, 130.84, 130.80, 128.7, 128.6, 127.40, 127.37, 125.8, 62.8, 59.1, 52.4, 38.6, 36.6; HRMS (ESI): m/z [M+H]+ calc’d for C_{20}H_{21}N_{4}O_{3} 365.16136, found 365.16189.

**Methyl 2-ethyl-1-oxo-4,8-diphenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazine-6-carboxylate (9.7)**

![Structure of Methyl 2-ethyl-1-oxo-4,8-diphenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazine-6-carboxylate](image)

1-Benzyl-5-ethyl-3-phenyl-6-oxoverdazyl (279 mg, 1.00 mmol) was reacted according to the general procedure for the cycloaddition reaction to yield a yellow oil (97.6 mg, 26%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.68-7.62 (d, J = 7.3 Hz, 2H), 7.48-7.35 (m, 7H), 7.32-7.26 (m, 1H), 5.68-5.62 (m, 1H), 4.37-4.30 (m, 1H), 3.91-3.80 (m, 1H), 3.77-3.68 (m, 1H), 3.64 (s, 3H), 2.84-2.75 (m, 1H), 2.59-2.49 (m, 1H), 1.34-1.27 (t, J = 7.1 Hz, 3H); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) δ 170.8, 153.4, 145.4, 141.2, 131.0, 130.7, 128.7, 128.6, 127.4, 127.3, 125.8, 62.8, 59.1, 52.4, 43.8, 38.5, 13.2; HRMS (ESI): m/z [M+H]+ calc’d for C_{21}H_{23}N_{4}O_{3} 379.17701, found 379.17710.

**Methyl 2-benzyl-8-methyl-1-oxo-4-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazine-6-carboxylate (9.8)**

![Structure of Methyl 2-benzyl-8-methyl-1-oxo-4-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazine-6-carboxylate](image)
1-Benzyl-5-ethyl-3-phenyl-6-oxoverdazyl (279 mg, 1.00 mmol) was reacted according to the general procedure for the cycloaddition reaction to yield a yellow oil (167 mg, 44%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.59-7.53 (d, $J = 7.5$ Hz, 2H), 7.51-7.46 (d, $J = 7.2$ Hz, 2H), 7.42-7.31 (m, 5H), 7.29-7.24 (m, 1H), 5.04-4.96 (d, $J = 15.0$ Hz, 1H), 4.75-4.67 (d, $J = 14.9$ Hz, 1H), 4.66-4.56 (m, 1H), 4.29-4.22 (dd, $J = 8.3$ Hz, 2.6 Hz, 1H), 3.32 (s, 3H), 2.50-2.41 (m, 1H), 2.16-2.01 (m, 1H), 1.41-1.36 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (100MHz, CDCl$_3$) $\delta$ 170.1, 153.7, 145.5, 137.8, 131.0, 130.7, 128.6, 128.4, 128.2, 127.4, 127.1, 62.6, 52.6, 52.4, 52.0, 37.1, 20.9; HRMS (ESI): $m/z$ [M+H]$^+$ calc’d for C$_{21}$H$_{23}$N$_4$O$_3$ 379.17701, found 379.17678.

Methyl 2-isopropyl-1-oxo-4-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazine-6-carboxylate (9.9)

1-Isopropyl -5-methyl-3-phenyl-6-oxoverdazyl (231 mg, 1.00 mmol) was reacted according to the general procedure for the cycloaddition reaction to yield yellow crystals mp 40-42 °C (209 mg, 66%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.68-7.63 (d, $J = 7.4$ Hz, 2H), 7.42-7.33 (m, 3H), 4.78-4.66 (septet, $J = 6.6$ Hz, 1H), 4.28-4.18 (m, 2H), 3.48 (s, 3H), 3.41-3.33 (m, 1H), 2.42-2.31 (m, 1H), 2.23-2.13 (m, 1H), 1.33-1.29 (d, $J = 6.7$ Hz, 3H), 1.28-1.24 (d, $J = 6.7$ Hz, 3H); $^{13}$C NMR (100MHz, CDCl$_3$) $\delta$ 171.0, 153.2, 145.4, 131.3, 130.5, 128.4, 127.2, 61.8, 52.0, 47.4, 43.9, 29.4, 20.1, 19.7; HRMS (ESI): $m/z$ [M+H]$^+$ calc’d for C$_{16}$H$_{21}$N$_4$O$_3$ 317.16136, found 317.16211.
9.3 Results and Discussion

With a new synthetic method in hand to readily allow the synthesis of 1,5-dialkyl-6-oxoverdazyl radicals with different substituents at N1 and N5, an additional level of substituent variability on verdazyl radical-derived compounds has been realized. In all the cycloadduct products and rearrangement reactions studied in the Georges lab thus far, a methyl group from the 1,5-dimethyl-6-oxoverdazyl radical starting material appears as a constant feature in all the derived compounds. By substituting another group for one of the methyl groups, new derivatives were a possibility (Scheme 9.2).

\[
R = \text{1}^\circ \text{alkyl}
\]

![Scheme 9-2. Envisioned new derivatizability of verdazyl radical-derived compounds.](image)

Since a methyl would be the smallest alkyl substituent possible, we assumed that the hydrogen atom abstraction in the formation of the 1,3-dipole would occur preferentially on the methyl side of an unsymmetrical verdazyl radical versus a sterically larger group. However, when the 1-ethyl-5-methyl-3-phenyl-6-oxoverdazyl radical 9.10 was subjected to cycloaddition reaction
conditions with methyl acrylate, a somewhat surprising product distribution was observed in the resultant cycloadduct products (Scheme 9-3).

Scheme 9-3. Observed product distribution from the reaction of 1-ethyl-5-methyl-3-phenyl-6-oxoverdazyl radical with methyl acrylate.

What was predicted to be the major product, 9.2, formed in only an 11% yield while the cycloadduct product 9.1, derived from the ethyl group participating in the 1,3-dipole formation, was found to form in 64% yield. This demonstrates a preference for the ethyl group in the disproportionation reaction by a factor of 5.8 to 1. This phenomenon was observed to occur with other alkyl groups as well to a lesser extent. The result suggests that these larger alkyl groups do not sterically stabilize the verdazyl radical; on the contrary, they seem to make it more reactive.

A series of unsymmetrically substituted verdazyl radicals were synthesized and subject to cycloaddition reaction conditions with methyl acrylate to observe the cycloaddition reaction product distributions (Table 9-1). Attempts to include 1-allyl-5-methyl-6-oxoverdazyl radical in this series were complicated by the fact that the allyl double bond acted as a dipolarophile leading to a mixture of cycloaddition products preventing any unambiguous reactivity comparisons to be made.
<table>
<thead>
<tr>
<th>Verdazyl Radical</th>
<th>Major Cycloadduct</th>
<th>Minor Cycloadduct</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="N-phthalimidazyl" /></td>
<td><img src="image" alt="N-phthalimidazyl" /></td>
<td><img src="image" alt="N-phthalimidazyl" /></td>
<td>5.8 : 1</td>
</tr>
<tr>
<td><img src="image" alt="N-phthalimidazyl" /></td>
<td><img src="image" alt="N-phthalimidazyl" /></td>
<td><img src="image" alt="N-phthalimidazyl" /></td>
<td>4.5 : 1</td>
</tr>
<tr>
<td><img src="image" alt="N-phthalimidazyl" /></td>
<td><img src="image" alt="N-phthalimidazyl" /></td>
<td><img src="image" alt="N-phthalimidazyl" /></td>
<td>2.8 : 1</td>
</tr>
<tr>
<td><img src="image" alt="N-phthalimidazyl" /></td>
<td><img src="image" alt="N-phthalimidazyl" /></td>
<td><img src="image" alt="N-phthalimidazyl" /></td>
<td>N/A</td>
</tr>
<tr>
<td><img src="image" alt="N-phthalimidazyl" /></td>
<td><img src="image" alt="N-phthalimidazyl" /></td>
<td><img src="image" alt="N-phthalimidazyl" /></td>
<td>1.7 : 1</td>
</tr>
</tbody>
</table>
Table 9-1. Unsymmetrical verdazyl radical derived cycloaddition reaction products with methyl acrylate and their product ratios.

Sterics, it appears, is not the only property of these substituents that affects reactivity. Given that these verdazyl radicals disproportionate by a hydrogen atom abstraction reaction, the bond dissociation energy of the C-H bond of interest needs to be considered. In the case of verdazyl radical 9.12, the preference for the benzyl side to have its hydrogen atom abstracted can be easily rationalized by the significantly weaker benzylic C-H bond despite the increased sterics involved.

The largest preference of 1,3-dipole formation over the methyl group observed occurred with the ethyl substituent seen in 9.10. The BDE of the C-H bond being abstracted is only slightly weaker with an ethyl group compared to methyl group because of the extra stabilization of generating a 2° carbon radical versus a 1° carbon radical. However, additional steric hindrance is a lot less than with a benzyl group (preference is 5.8 : 1 for ethyl versus 2.8 : 1 with benzyl) so a good balance between a lower BDE and increased sterics was struck to explain the ethyl group having the highest selectivity. Verdazyl radical 9.11 showed a ratio of 4.5 : 1 for n-propyl vs a methyl group, with the n-propyl group having a comparable BDE to an ethyl group for its abstractable hydrogen but the increase in sterics resulted in a slightly lower selectivity.

The high preference of 1,3-dipole formation for an ethyl group was confirmed with verdazyl radical 9.14 which was synthesized and reacted as a direct comparison between the reactivity of a benzyl group versus an ethyl group (1.7 : 1 ethyl versus benzyl). Verdazyl radical 9.13, synthesized by Brook’s modified Milcent methodology, was of interest to study since Hicks et. al. stated that the di-isopropyl verdazyl radical is more stable than its dimethyl counterparts.
Verdazyl radical 9.13 afforded only the cycloadduct product from a methyl side azomethine imine formation with no product observed from a reaction of the isopropyl group. Although the latter group’s C-H bond is weaker than the methyl’s, the sterics were too significant in the isopropyl group to surmount to give any hydrogen atom abstraction. This result proved consistent with Hicks’ assertion that isopropyl substituted verdazyl radicals are more stable than the methyl derivative.

As a rough quantification of the opposing BDEs and sterics at play, Table 9-2 draws a comparison between approximated relative values of BDE (sourced from comparable alkyl examples) and steric A-values of substituents used in the above series.

<table>
<thead>
<tr>
<th>Substituent</th>
<th>BDE (kcal/mol)</th>
<th>Addition sterics relative to Me (A-values in kcal/mol)</th>
<th>Ratio of cycloadduct relative to methyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl</td>
<td>101.1</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Ethyl</td>
<td>98.6</td>
<td>1.74</td>
<td>5.8</td>
</tr>
<tr>
<td>n-Propyl</td>
<td>98.6</td>
<td>1.79</td>
<td>4.5</td>
</tr>
<tr>
<td>Benzyl</td>
<td>89.7</td>
<td>2.8</td>
<td>2.8</td>
</tr>
<tr>
<td>i-Propyl</td>
<td>96.5</td>
<td>3.48</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 9-2. Estimated relative BDEs and sterics of substituents

Table 9-2 provides a crude approximation of the competing factors involved in the selectivity of the 1,3-dipole formation by disproportionation. The BDE of the benzyl substituent is significantly lower than other examples and would dictate virtually exclusive benzyl side
product. However, with a steric A-value of 2.8, the approach of the oxidant verdazyl radical clearly starts to become significantly hindered. The isopropyl group, with the lowest BDE of the alkyl examples, is clearly overcome by the steric contribution with the highest A-value (3.48) yielding no isopropyl side selectivity. It should be noted that the rationale used herein to explain these selectivities are under the assumption that azomethine imine formation proceeds under kinetic control. A situation where the azomethine imine formation is reversible and selectivity is under thermodynamic control cannot be ruled out since this disproportionation mechanism has not been studied in great detail.

9.4 Summary

Using the newly developed synthesis for alkyl substituted verdazyl radicals\(^1\), a new mode of derivatizing verdazyl radical-derived compounds was thwarted by surprising selectivity issues observed between differing N1 and N5 alkyl substituents on unsymmetrical verdazyl radicals. A series of unsymmetrically substituted 1,5-dialkyl verdazyl radicals were synthesized and exposed to cycloaddition reaction conditions to observed cycloadduct product distributions and hence site selectivity for the disproportionation reaction. Despite the greater sterics of the larger alkyl substituents normally associated with stabilization of radicals compared to methyl, the majority of cycloadduct products isolated were derived from 1,3-dipoles which formed on the larger alkyl groups due to the lower BDEs of hydrogen atom abstraction, which facilitated preferential disproportionation. The results demonstrated interplay between lower BDEs, promoting hydrogen atom abstraction, and greater sterics inhibiting it. The example of isopropyl versus methyl showed that isopropyl pushed the limits of allowed steric crowding and essentially blocked hydrogen atom abstraction at the site affording only the methyl side cycloadduct product.
9.5 References


Chapter 10

10 Triphenyl Verdazyl Radicals’ Reactions with Alkynes

10.1 Introduction and Objective

The majority of verdazyl radical based research in the Georges lab has centered on 6-oxoverdazyls. It is these 6-oxoverdazyl radicals which disproportionate to form azomethine imines and subsequently undergo cycloaddition with dipolarophiles that have served as the backbone for our entry into N-heterocycle chemistry. As discussed earlier in section 1.2 of this thesis, most verdazyl radicals can be readily categorized into two major groups: those containing a sp\(^2\) centre at the 6-position, as with 6-oxoverdazyl radicals, and those containing a sp\(^3\) center exemplified by triphenyl verdazyl radical \textbf{10.1}. Although reports of verdazyl radicals’ reactivity has been sparse in the literature, an interesting example for the sp\(^3\) class was shown by Neugebauer et al.\(^1\) in 1972 (Scheme 10-1).

![Scheme 10-1](image)

\textbf{Scheme 10-1.} Decomposition of triphenyl verdazyl radical.

Although no mechanistic explanation was offered, what made this thermal decomposition noteworthy is the presence of leucoverdazyl \textbf{10.2} along with \textbf{10.3} in a 1:1 ratio. This strikingly resembles the disproportionation of 6-oxoverdazyl radicals, only here the analogous oxidized
complement, presumably the intra-ring azomethine imine 10.4, is not stable and rearranges to 10.3 depicted in Scheme 10-2.

**Scheme 10-2.** Decomposition of triphenyl verdazyl radical to a triazole via an assumed azomethine imine.

If 10.4 were indeed an intermediate, using a dipolarophile to trap it would yield a very unique cycloadduct scaffold. Unfortunately, heating the triphenyl verdazyl radical in the presence of a dipolarophile did not lead to a cycloaddition. Interestingly however, very electron deficient alkynes were shown to react with this triphenyl verdazyl to afford 1-(phenyldiazenyl)isoquinoline-3,4-dicarboxylates 10.5. These compounds are quite attractive to synthesize since isoquinolines are a common feature of many alkaloids. They also appear as structural motifs in many drugs including quinapril, an antihypertensive, papaverin, a vasodilator and dimethisoquin, an anesthetic.

**Figure 10-1.** 1-(Phenyldiazenyl)isoquinoline-3,4-dicarboxylates
A series of these compounds were synthesized from various alkynes and different derivatives of triphenyl verdazyl radicals to test the scope and deduce the mechanism of this peculiar reaction.

10.2 Experimental

**Materials and Equipment:** All reagents and ACS grade solvents were purchased from Sigma-Aldrich or VWR unless otherwise stated. Column chromatography was performed with Silica Gel P60 (mesh size 40-63 µm) obtained from Silicycle. Thin layer chromatography (TLC) plates were obtained from EMD with Silica Gel 60 F\textsubscript{254} and visualized under UV (254 nm) light. NMR spectra were recorded on a Bruker Avance III spectrometer at 23 °C, at 400 MHz for \textsuperscript{1}H NMR and 100 MHz for \textsuperscript{13}C NMR or on a Varian Unity INOVA-500 spectrometer at 23 °C, operating at 500 MHz for \textsuperscript{1}H NMR and 125 MHz for \textsuperscript{13}C NMR. Chemical shifts (δ) are reported in parts per million (ppm) referenced to tetramethylsilane (0 ppm) for \textsuperscript{1}H NMR spectra and CDCl\textsubscript{3} (77.0 ppm) for \textsuperscript{13}C NMR. Coupling constants (J) are reported in hertz (Hz). Spin multiplicities are indicated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Accurate mass determinations (HRMS) were carried out by the AIMS lab, Department of Chemistry, University of Toronto, using a Waters GC TOF mass spectrometer with an ESI source, MS/MS and accurate mass capabilities, associated with an Agilent 1100 capillary LC system. FT-IR spectra were acquired on a Nicolet Avatar 360 spectrometer using pellets prepared with KBr or as thin films on NaCl cells. Melting points were determined on an Electrothermal capillary melting point apparatus and are uncorrected. Single crystal X-ray structural determinations were carried out at the X-ray facility, Department of Chemistry, University of Toronto, on a Bruker-Nonius Kappa-CCD diffractometer using monochromated Mo-Kα radiation. Measurements were made using a combination of Φ and ω scans with κ offsets to fill the Ewald sphere. The data were processed using the Denzo-SMN
package. Absorption corrections were carried out using SORTAV. The structure was solved and refined using SHELXTL V6.1 for full-matrix least-squares refinement that was based on $F^2$. All hydrogen atoms were included in the calculated positions and allowed to refine in the riding-motion approximation with U-iso-tied to the carrier atom.

**General Formazan Synthesis:** 1-(4-Chlorobenzylidene)-2-phenylhydrazine (2.00 g, 8.67 mmol) was dissolved in 50 mL of methanol in a 250 mL round bottom flask. To this was added a buffer solution composed of 35 mL methanol, 1.5 g NaOH and 1.2 g NaOAc. This solution was then cooled to 0 °C in an ice bath. Phenyl diazonium chloride was prepared by the dropwise addition of 1.3 mL of an aqueous solution of 0.32 g of NaNO$_2$ to a cooled solution (0 °C) of 0.41 g aniline in 2.1 mL of 6M HCl. The phenyl diazonium chloride salt solution was subsequently added dropwise to the solution of 1(4-chlorobenzylidene)-2-phenylhydrazine resulting in a deep red colour. The reaction was allowed to warm to room temperature after 1 hour of stirring and was taken up in 200 mL of EtOAc and washed 3 times with 200 mL portions of water. The crude extract was dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuo. The crude product was isolated using silica gel column chromatography (1:9 EtOAc in hexanes as the eluent) and the purified product was recrystallized in 1:19 EtOAc in hexanes to yield compound 10.8.

**General Verdazyl Radical and Isoquinoline Synthesis:** 1,3,5-Triphenylformazan (1.00 g, 3.33 mmol) was dissolved in 50 mL of DMF in a 250 mL round bottom flask. To this stirred solution, a 37% formaldehyde solution (3.8 mL, 51 mmol) and 5.2 mL of 3M KOH(aq) was added. The reaction was allowed to stir under an O$_2$ atmosphere for 1 hour at room temperature. Within 15 minutes a colour change from deep red to deep green occurred indicating the formation of the 1,3,5-triphenyl verdazyl radical. Following 1 hour of stirring the reaction was taken up in 200
mL of EtOAc and washed 3 times with 200 mL portions of water. The crude extract was dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuo. The crude verdazyl radical was purified using silica gel column chromatography (1:9 EtOAc in hexanes as the eluent).

A portion of this freshly prepared verdazyl radical (300 mg, 0.96 mmol) was dissolved in 1-2 mL of THF in a 10 mL round bottom flask. Ten equivalents of DMAD (1.36 g, 1.18 mL, 9.57 mmol) was added to this stirred solution and heated at 60 °C for 24 hours. Following this, the solvent and part of the DMAD was evaporated in vacuo and the crude product was isolated using silica gel column chromatography (1:3 EtOAc in hexanes as the eluent) and recrystallized in 1:3 EtOAc in hexanes to yield compound 10.10.

3-(2-Chlorophenyl)-1,5-diphenylformazan (10.6)

1-(2-Chlorobenzylidene)-2-phenylhydrazine (2.00g, 8.67 mmol) was reacted according to the general formazan synthesis procedure to yield red crystals (2.35 g, 81%) mp 92-94 °C; FT-IR (υ, cm⁻¹, KBr) 3310, 3054, 1601, 1564, 1501, 1241; ¹H NMR (400 MHz, CDCl₃) δ 7.84 (s, 1H), 7.79-7.75 (d, J = 7.2 Hz, 2H), 7.63-7.59 (m, 4H), 7.43-7.41 (m, 3H), 7.28-7.24 (m, 4H), 7.02-6.97 (t, J = 7.1 Hz, 1H); ¹³C NMR (100MHz, CDCl₃) δ 153.3, 152.7, 147.7, 143.8, 142.4, 135.3, 131.5, 130.5, 129.2, 128.7, 127.1, 126.4, 122.8, 122.3, 118.6; HRMS (ESI): m/z [M+H]⁺ calc’d for C₁₉H₁₆ClN₄ 335.10635, found 335.10691.
3-(3-Chlorophenyl)-1,5-diphenylformazan (10.7)

1-(3-Chlorobenzylidene)-2-phenylhydrazine (2.00g, 8.67 mmol) was reacted according to the general formazan synthesis procedure to yield red crystals (2.53 g, 87%) mp 139-141 °C; FT-IR (v, cm\(^{-1}\), KBr) 3065, 2916, 2848, 1592, 1514, 1454, 1421, 1283, 1229, 1074; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.10-8.08 (t, J = 7.1 Hz, 1H), 8.02-7.98 (dt, J = 7.7 Hz, J = 1.3 Hz, 1H), 7.67-7.63 (d, J = 7.7 Hz, 4H), 7.48-7.42 (m, 4H), 7.37-7.31 (m, 1H), 7.31-7.25 (m, 4H); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 147.6, 139.7, 139.3, 134.4, 129.6, 129.5, 127.8, 127.5, 125.7, 123.8, 118.9; HRMS (ESI): \(m/z\) [M+H]\(^+\) calc’d for C\(_{19}\)H\(_{16}\)ClN\(_3\) 335.10635, found 335.10695.

3-(4-Chlorophenyl)-1,5-diphenylformazan (10.8)

1-(4-Chlorobenzylidene)-2-phenylhydrazine (2.00g, 8.67 mmol) was reacted according to the general formazan synthesis procedure to yield red crystals (2.47 g, 85%) mp 98-100 °C; FT-IR (v, cm\(^{-1}\), KBr) 3061, 1599, 1488, 1453, 1236, 1184, 1091; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.09-8.06 (m, 2H), 7.68-7.66 (m, 4H), 7.49-7.45 (m, 4H), 7.41-7.39 (m, 2H), 7.32-7.29 (m, 3H); \(^{13}\)C
NMR (100MHz, CDCl$_3$) δ 147.6, 140.1, 135.9, 133.3, 129.3, 129.1, 128.4, 128.1, 127.5, 126.9, 118.7; HRMS (ESI): m/z [M+H]$^+$ calc’d for C$_{19}$H$_{16}$ClN$_4$ 335.10635, found 335.10692.

3-(4-Methoxyphenyl)-1,5-di-p-tolylformazan (10.9)

![Chemical structure](https://example.com/structure.png)

1-(4-Methoxybenzylidene)-2-p-tolylhydrazine (2.08 g, 8.67 mmol) was reacted according to the general formazan synthesis procedure, substituting 4-methylaniline for aniline to yield red crystals (2.39 g, 77%) mp 122-124 ºC; FT-IR (v, cm$^{-1}$, KBr) 3065, 2922, 2853, 1605, 1508, 1463, 1251, 1224, 1026; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.07-8.04 (d, J = 8.7 Hz, 2H), 7.57-7.55 (d, J = 8.4 Hz, 4H), 7.25-7.23 (m, 5H), 6.98-6.96 (d, J = 8.7 Hz, 4H), 3.87 (s, 3H), 2.39 (s, 6H); $^{13}$C NMR (100MHz, CDCl$_3$) δ 159.2, 145.8, 140.8, 137.1, 130.4, 129.8, 127.0, 118.4, 113.6, 55.2, 21.1; HRMS (ESI): m/z [M+H]$^+$ calc’d for C$_{22}$H$_{23}$N$_4$O 359.18719, found 359.18748.

(E)-Dimethyl-1-(phenyldiazényl)isoquinoline-3,4-dicarboxylate (10.10)

![Chemical structure](https://example.com/structure.png)
1,3,5-Triphenylformazan (1.00 g, 3.33 mmol) was reacted according to the general verdazyl radical and isoquinoline synthesis procedure to yield red prismatic crystals (207 mg, 62%) mp 104-107 °C; FT-IR (ν, cm\(^{-1}\), KBr) 3066, 2953, 1744, 1715, 1614, 1576; \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 8.79-8.75 (d, J = 8.3 Hz, 1H), 8.20-8.16 (m, 2H), 8.06-8.02 (d, J = 8.4 Hz, 1H), 7.95-7.89 (t, J = 7.4 Hz, 1H), 7.89-7.83 (t, J = 7.5 Hz, 1H), 7.62-7.57 (m, 3H), 4.13 (s, 3H), 4.04 (s, 3H); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) δ 167.6, 165.5, 159.7, 153.2, 137.7, 135.1, 133.1, 132.5, 130.4, 130.0, 129.3, 125.9, 125.8, 125.5, 124.2, 53.34, 53.31; HRMS (ESI): m/z [M+H]\(^+\) calc’d for C\(_{19}\)H\(_{16}\)N\(_3\)O\(_4\) 350.11408, found 350.11496.

(E)-Dimethyl-8-chloro-1-(phenyldiazenyl)isoquinoline-3,4-dicarboxylate (10.11)

\[
\text{MeO}_2\text{C} \quad \text{N} \quad \text{Ph} \\
\text{MeO}_2\text{C} \quad \text{Cl}
\]

Compound 10.6 (1.11 g, 3.33 mmol) was reacted according to the general verdazyl radical and isoquinoline synthesis procedure to yield red prismatic crystals (180 mg, 49%) mp 138-140 °C; FT-IR (ν, cm\(^{-1}\), KBr) 3076, 2954, 2925, 1733, 1600, 1568, 1549; \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 8.15-8.10 (m, 2H), 7.95-7.91 (d, J = 8.4 Hz, 1H), 7.90-7.84 (d, J = 7.5 Hz, 1H), 7.80-7.74 (t, J = 8.0 Hz, 1H), 7.61-7.57 (m, 3H), 4.11 (s, 3H), 4.02 (s, 3H); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) δ 167.2, 164.8, 162.4, 152.6, 137.8, 136.9, 132.74, 132.66, 132.04, 131.99, 129.1, 128.9, 124.6, 124.3, 121.8, 53.3, 53.2; HRMS (ESI): m/z [M+H]\(^+\) calc’d for C\(_{19}\)H\(_{15}\)ClN\(_3\)O\(_4\) 384.07511, found 384.07411.

(E)-Dimethyl-6-chloro-1-(phenyldiazenyl)isoquinoline-3,4-dicarboxylate (10.12)
Compound **10.8** (1.11g, 3.33 mmol) was reacted according to the general verdazyl radical and isoquinoline synthesis procedure to yield red prismatic crystals (213 mg, 58%) mp 131-132 °C; FT-IR (v, cm⁻¹, KBr) 3048, 3021, 2954, 1732, 1606, 1568, 1241; ¹H NMR (400 MHz, CDCl₃) δ 8.74-8.71 (d, J = 9.0 Hz, 1H), 8.18-8.14 (m, 2H), 8.04-8.03 (d, J = 2.0 Hz, 1H), 7.81-7.77 (dd, J = 9.0 Hz, 2.0 Hz, 1H), 7.64-7.56 (m, 3H), 4.13 (s, 3H), 4.04 (s, 3H); ¹³C NMR (100MHz, CDCl₃) δ 166.9, 165.1, 159.5, 139.3, 139.2, 135.8, 133.2, 131.1, 129.1, 128.4, 127.4, 124.3, 124.1 123.9, 53.31, 53.27; HRMS (ESI): m/z [M+H]⁺ calc’d for C₁₉H₁₅ClN₃O₄ 384.0745, found 384.0729.

(E)-Dimethyl-5-chloro-1-(phenyldiazenyl)isoquinoline-3,4-dicarboxylate (**10.13**)

Compound **10.7** (1.11g, 3.33 mmol) was reacted according to the general verdazyl radical and isoquinoline synthesis procedure to yield red prismatic crystals (95.5 g, 28%) mp 40-42 °C; FT-IR (v, cm⁻¹, KBr) 2950, 1733, 1600, 1446, 1384, 1257; ¹H NMR (400 MHz, CDCl₃) δ 8.81-8.78 (dd, J = 8.4 Hz, 1.2 Hz, 1H), 8.19-8.15 (m, 2H), 8.01-7.97 (dd, J = 7.4 Hz, 1.2 Hz, 1H), 7.80-
7.74 (t, J = 8.0 Hz, 1H), 7.63-7.59 (m, 3H), 4.10 (s, 3H), 4.03 (s, 3H); $^{13}$C NMR (100MHz, CDCl$_3$) δ 167.8, 165.1, 159.9, 153.2, 139.5, 134.7, 133.3, 132.3, 131.2, 130.1, 129.3, 128.0, 127.8, 125.3, 124.3, 53.4, 53.3; HRMS (ESI): m/z [M+H]$^+$ calc’d for C$_{19}$H$_{15}$ClN$_3$O$_4$ 384.07511, found 384.07558.

**(E)-Dimethyl-7-chloro-1-(phenyldiazenyl)isoquinoline-3,4-dicarboxylate (10.14)**

![Structure](image)

Compound 10.7 (1.11g, 3.33 mmol) was reacted according to the general verdazyl radical and isoquinoline synthesis procedure to yield red prismatic crystals (103 mg, 28%) mp 139-141 °C; FT-IR (ν, cm$^{-1}$, KBr) 3057, 2956, 1732, 1717, 1637, 1599, 1575, 1442, 1273; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.78-8.75 (d, J = 2.0 Hz, 1H), 8.21-8.16 (m, 2H), 8.02-7.99 (d, J = 9.0 Hz, 1H), 7.88-7.84 (dd, J = 9.0 Hz, 2.1 Hz, 1H), 7.64-7.59 (m, 3H), 4.12 (s, 3H), 4.04 (s, 3H); $^{13}$C NMR (100MHz, CDCl$_3$) δ 167.0, 165.1, 158.4, 153.0, 138.1, 136.5, 133.4, 133.2, 129.9, 129.4, 129.2, 127.0, 126.5, 124.8, 124.2, 53.27, 53.25; HRMS (ESI): m/z [M+H]$^+$ calc’d for C$_{19}$H$_{15}$ClN$_3$O$_4$ 384.07511, found 384.07498.

**(E)-Di-tert-butyl-1-(phenyldiazenyl)isoquinoline-3,4-dicarboxylate (10.15)**

![Structure](image)
1,3,5-Triphenylformazan (1.00g, 3.33 mmol) was reacted according to the general verdazyl radical and isoquinoline synthesis procedure, substituting DMAD with DTBAD, to yield red prismatic crystals (261 g, 63%) mp 109-112 °C; FT-IR (v, cm\(^{-1}\), KBr) 3007, 2979, 2930, 1735, 1714, 1602, 1570, 1500, 1249; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.72-8.68 (d, J = 8.3 Hz, 1H), 8.18-8.14 (m, 2H), 8.14-8.11 (d, J = 8.4 Hz, 1H), 7.91-7.85 (t, J = 7.8 Hz, 1H), 7.82-7.77 (t, J = 7.7 Hz, 1H), 7.62-7.58 (m, 3H), 1.70 (s, 9H), 1.68 (s, 9H); \(^1^3\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 166.0, 164.4, 159.1, 152.9, 139.8, 135.0, 132.6, 131.8, 129.8, 129.3, 129.1, 125.4, 125.2, 125.1, 123.9, 83.2, 82.9, 28.0; HRMS (ESI): \(m/z\) [M+H]\(^+\) calc'd for C\(_{25}\)H\(_{28}\)N\(_3\)O\(_4\) 434.20798, found 434.20837.

(E)-Ethyl-4-phenyl-1-(phenyldiazenyl)isoquinoline-3-carboxylate (10.16)

1,3,5-Triphenylformazan (1.00g, 3.33 mmol) was reacted according to the general verdazyl radical and isoquinoline synthesis procedure, substituting DMAD with EPP, to yield red prismatic crystals (102 mg, 28%) mp 135-136 °C; FT-IR (v, cm\(^{-1}\), KBr) 3065, 2978, 2928, 1732, 1613, 1555, 1384; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.83-8.79 (d, J = 7.6 Hz, 1H), 8.21-8.16 (m, 2H), 7.79-7.72 (m, 3H), 7.61-7.57 (m, 3H), 7.55-7.48 (m, 3H), 7.42-7.38 (m, 3H), 4.17-4.10 (q, J = 7.2 Hz, 2H), 1.03-0.98 (t, J = 7.2 Hz, 3H); \(^1^3\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 166.6, 158.5, 153.1, 141.4, 137.6, 135.8, 135.1, 132.4, 131.1, 129.7, 129.0, 128.9, 128.1, 128.0, 126.4, 125.5, 125.3, 123.9, 61.3, 13.5; HRMS (ESI): \(m/z\) [M+H]\(^+\) calc’d for C\(_{25}\)H\(_{25}\)N\(_3\)O\(_2\) 382.15555, found 382.15613.
(E)-Dimethyl 6-methoxy-1-(p-tolyl diazenyl)isoquinoline-3,4-dicarboxylate (10.17)

![Chemical Structure]

Compound 10.9 (1.19g, 3.33 mmol) was reacted according to the general verdazyl radical and isoquinoline synthesis procedure to yield red crystals (215 mg, 57%) mp 132-134 °C; FT-IR (ν, cm\(^{-1}\), KBr) 3429, 3001, 2955, 1731, 1615, 1571, 1467; \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 8.71-8.69 (d, J = 9.3 Hz, 1H), 8.08-8.06 (d, J = 8.3 Hz, 2H), 7.46-7.43 (dd, J = 9.3 Hz, J = 2.5 Hz, 1H), 7.39-7.37 (d, J = 8.3 Hz, 2H), 7.14-6.85 (br, 1H), 4.11 (s, 3H), 4.02 (s, 3H), 4.00 (s, 3H), 2.49 (3H, s); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) δ 167.8, 165.6, 162.3, 159.0, 151.3, 143.8, 139.0, 129.7, 128.1, 127.6, 124.1, 122.8, 121.4, 103.0, 55.6, 53.09, 53.08, 21.6; HRMS (ESI): m/z [M+H]\(^+\) calc’d for C\(_{21}\)H\(_{20}\)N\(_{3}\)O\(_{5}\) 394.14030, found 394.14122.

10.3 Results and Discussion

Due to the resemblance of Neugebauer’s 1,3,5-triphenyl verdazyl radical disproportionation reaction to the 6-oxoverdazyl radical disproportionation reaction in forming an azomethine imine, we inferred an azomethine imine intermediate 10.4 in Neugebauer’s reaction which, without a suitable dipolarophile present in solution, went on to form triazole 10.3. Using methyl acrylate, as well as styrene, attempts were made at trapping this proposed azomethine imine by 1,3-dipolar,cycloaddition reaction using our standard cycloaddition conditions in anticipation of products 10.18 and 10.19, respectively.
Figure 10-2. Anticipated cycloadducts of triphenyl verdazyl radicals with dipolarophiles.

These attempts were nevertheless unfruitful. Out of both reactions, upon workup and chromatography, a slew of products were isolated with the major two being those reported by Neugebauer. The others were not identified and did not match the proposed structures of the cycloadducts. Clearly these two reagents had little effect on the default reaction. Dimethyl acetylene dicarboxylate (DMAD) was subsequently used as a dipolarophile and a red solid was isolated in 62% yield after heating at 60 °C for 24 hours. Characterization data for this isolated compound was inconsistent with the proposed cycloadduct structure 10.20.
Scheme 10-3. Anticipated cycloadduct with DMAD with a proposed mechanism for its formation.

Using single crystal X-ray diffraction, the red compound’s structure was determined to be dimethyl-1-(phenyldiazenyl)isoquinoline-3,4-dicarboxylate 10.10 (Scheme 10-4). In an effort to elucidate the mechanism of this unforeseen transformation a series of chlorine substituted verdazyl radicals were made to determine where all of the atoms in the product were coming from. Chlorine atoms were substituted at the ortho, meta and para positions of the 3-phenyl group of 1,3,5-triphenyl verdazyl and then observed where they ended up in the final products. The results of these experiments are shown in entries 4-6 in Table 10-1. The ortho-chloro afforded a 5-chloro substituted isoquinoline, the para ends up giving the 8-chloro product and the meta derivative gave 2 regioisomers given that the aryl bond can rotate, with the
regioisomers forming in approximately a 1:1 ratio. These results allowed us to see how the final products came together and enabled us to propose the mechanism shown in Scheme 10-4.

![Scheme 10-4](image)

\( \text{V}^* = \text{1,3,5-triphenylverdazyl radical} \)

**Scheme 10-4.** Postulated mechanism for the formation of isoquinoline products derived from a triphenyl verdazyl radical.

The mechanism begins with the verdazyl radical directly attacking the low energy LUMO of the alkyne to form a vinyl radical **10.21**. The unstable vinyl radical goes on to react with the adjacent phenyl ring to form the radical shown in the second step as intermediate **10.22**, which is stabilized by delocalized. Another equivalent of verdazyl radical then abstracts a hydrogen atom to reform the benzene ring, a driving force to give the dihydrotetrazinoisoquinoline fused ring system **10.23**. The reduced verdazyl radical equivalent is oxidized in air back to a verdazyl.
radical. The fused ring system 10.23 breaks down via a retro-Diels-Alder reaction to yield the final product 10.10.

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<th>Alkyne</th>
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<th>Yield (%)</th>
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</table>
A series of these 1-(phenyldiazenyl)isoquinoline products were synthesized in yields ranging from 28% to 63%. In order to get a moderate yield, alkynes with two EWGs needed to be used. Product 10.16 was the lowest yielding example made with ethyl phenyl propiolate (EPP) having only one EWG. The reaction with EPP gave only one regioisomer 10.16 (orientation confirmed by X-ray diffraction), demonstrating this reaction proceeds regioselectively. Entry 5 led to two products in a near 1:1 ratio with a total yield of 54%. The two possible orientations of the 3-(3-chlorophenyl) group allow for two possible sites of attack for the vinyl radical 10.21 (Scheme 10.4).

An interesting extension of this chemistry would be to use verdazyl radicals with aromatic heterocycles at the C3 position. This would lead to more exotic heterocyclic ring systems, such as naphthyridines in the case of pyridyl derivatives and fused thienopyridines and furanopyridines with thiophene and furan derivatives, respectively.
Unfortunately, the thiophene and furan substituted verdazyl radicals, unreported in the literature, proved elusive to synthesize with known methods. All three pyridyl derivatives, 2, 3, and 4-pyridyl, were prepared using literature procedures, however they were observed to react orders of magnitude more rapidly than their phenyl counterparts. Upon addition of DMAD the characteristic red colour was observed within seconds but TLC did not show a clean transformation, instead, the result was a plethora of products. The reactions were repeated under dilute conditions with only one equivalent of DMAD at 0 °C, however, isolation of the reaction products was not accomplished cleanly enough for unambiguous characterization.

10.4 Summary

To conclude, a unique reactivity of verdazyl radicals with alkynes is demonstrated herein resulting in 1-(phenylidazeny1)isoquinolines. A series of these isoquinolines was generated showing that very electron deficient alkynes produce the highest yields. These verdazyl radicals are made in two steps starting from a hydrazone thus providing a quick and easy access to this class of isoquinolines. To propose a mechanism, a series of systematically chloro-substituted verdazyl radicals was reacted with DMAD. The mechanism shown for the formation of these compounds is consistent with the all the substitution patterns observed in the products and
involves an intramolecular rearrangement via radical intermediates followed by a retro Diels Alder fragmentation.

10.5 References

Chapter 11

11 Verdazyl Radicals as Substrates for Diversity Oriented Synthesis

11.1 Introduction and Objective

As described in chapter 5, verdazyl radicals have been shown to undergo a disproportionation to generate azomethine imines. These azomethine imines undergo 1,3-dipolar cycloaddition reactions with alkenes, as well as alkynes affording tetrahydropyrazolotetrazinones and dihydropyrazolotetrazinones, respectively, with various substitutions patterns.\textsuperscript{1,2} Many of these first generation cycloadduct compounds derived from verdazyl radicals have been shown in the preceding chapters to undergo subsequent rearrangement reactions. These rearrangement reactions occurred depending upon the substituents on the cycloadducts and the conditions they were exposed to leading to an array of N-heterocycles as second generation compounds.\textsuperscript{2,3} Figure 11-1 gives a summary of the assortment of first and second generation N-heterocycles generated to date by the Georges lab. In addition to the compounds shown in Figure 11-1 derived from the 1,5-dimethyl-3-phenyl-6-oxoverdazyl radical, these reactions have been demonstrated with verdazyl radicals with variable substituents at the N1,C3 and N5 positions.
Figure 11-1. Summary of N-heterocycles synthesized to date starting with 1,5-dimethyl-3-phenyl-6-oxoverdazyl radical.

The capacity to generate many different types of heterocyclic scaffolds in only two steps from a common starting material fits in well with the concept of diversity oriented synthesis (DOS). As discussed in chapter 4, the central tenet of DOS is the generation of chemical libraries containing structurally diverse scaffolds as opposed to just varying appended functional groups. The library of compounds anticipated by DOS is one with access to a wide sampling of chemical space.
through structural diversity used towards non-specific biological probing with the goal of finding a biologically active compound. Drug-like properties or molecular motifs, typically seen as biologically active, are preferred library candidates. These candidates include nitrogen containing heterocyclic compounds.\(^5\)

The diversity built into such a library can be derived from several generations of compounds. The first generation can be made by a common reaction with a wide variety of starting materials providing a common molecular backbone as with, for example, our cycloaddition reactions. Subsequently, transformations on these first generation compounds can lead to several classes of second generation heterocyclic scaffolds, exemplified with the cycloadduct rearrangement reactions. A further expansion in the library of these compounds can occur if functionalities present in the compounds are derivatized. This chapter outlines the use of compounds previously synthesized in preceding chapters, as well as, a complement of additional compounds in testing against acute myeloid leukemia and multiple myeloma cell lines.

11.2 Experimental

**Materials and Equipment:** All reagents and ACS grade solvents were purchased from Sigma-Aldrich or VWR unless otherwise stated. Column chromatography was performed with Silica Gel P60 (mesh size 40-63 µm) obtained from Silicycle. Thin layer chromatography (TLC) plates were obtained from EMD with Silica Gel 60 F\(_{254}\) and visualized under UV (254 nm) light. NMR spectra were recorded on a Bruker Avance III spectrometer at 23 °C, at 400 MHz for \(^1\)H NMR and 100 MHz for \(^13\)C NMR or on a Varian Unity INOVA-500 spectrometer at 23 °C, operating at 500 MHz for \(^1\)H NMR and 125 MHz for \(^13\)C NMR. Chemical shifts (\(\delta\)) are reported in parts per million (ppm) referenced to tetramethylsilane (0 ppm) for \(^1\)H NMR spectra and CDCl\(_3\) (77.0 ppm) for \(^13\)C NMR. Coupling constants (\(J\)) are reported in hertz (Hz). Spin multiplicities are
indicated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad).

**Dimethyl 2-methyl-4-(3-nitrophenyl)-1-oxo-2,8-dihydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazine-6,7-dicarboxylate (11.1)**

![Chemical Structure]

1,5-Dimethyl-3-(3-nitrophenyl)-6-oxoverdazyl (2.30 g, 9.27 mmol) was dissolved in 10 mL of THF in a 25 mL round-bottom flask. Dimethyl acetylene dicarboxylate (6.60 g, 5.70 mL, 46.4 mmol, 5 eq.) was added and the solution was refluxed for 48 h. The reaction solution was cooled to ambient temperature, and the unreacted DMAD was removed *in vacuo*. The product was isolated by silica column chromatography (1:2 ethyl acetate/hexanes) to yield a yellow solid (2.47 g, 68%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.49-8.46 (t, J = 1.9 Hz, 1H), 8.31-8.27 (d, J = 8.3 Hz, 1H), 7.97-7.93 (dt, J = 7.8 Hz, 1.2 Hz, 1H), 7.61-7.55 (t, J = 8.0 Hz, 1H), 4.84 (s, 2H), 3.71 (s, 3H), 3.41 (s, 3H), 3.31 (s, 3H).

**2-Methyl-6-phenyl-4-(pyridin-3-yl)-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazine-1-one (11.2)**
1,5-Dimethyl-3-(3-pyridyl)-6-oxoverdazyl (500 mg, 2.46 mmol) was dissolved in 3 mL of THF in a 10 mL round-bottom flask. Styrene (1.41 mL, 12.3 mmol, 5 eq.) and the solution was refluxed for 48 h. The reaction solution was cooled to ambient temperature and the unreacted styrene was removed in vacuo. The product was isolated by silica column chromatography (1:2 ethyl acetate/hexanes) to yield a yellow oil (426 mg, 57%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.65-8.63 (d, $J = 1.9$ Hz, 1H), 8.53-8.51 (dd, $J = 4.8$ Hz, 1.6 Hz, 1H), 7.64-7.60 (dt, $J = 8.0$ Hz, 2.0 Hz, 1H), 7.19-7.10 (m, 4H), 6.95-6.91 (m, 2H), 4.71-4.66 (dd, $J = 8.7$ Hz, 5.7 Hz, 1H), 4.34-4.26 (m, 1H), 3.74-3.66 (m, 1H), 3.25 (s, 3H), 2.64-2.54 (m, 1H), 2.26-2.16 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 154.9, 150.8, 148.6, 144.9, 139.0, 134.6, 128.4, 128.2, 127.8, 127.3, 122.8, 66.6, 45.0, 36.7, 33.6.

4-Benzyl-2-methyl-6-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (11.3)

1,5-Dimethyl-3-(3-benzyl)-6-oxoverdazyl (400 mg, 1.84 mmol) was dissolved in 3 mL of THF in a 10 mL round-bottom flask. Styrene (1.05 mL, 9.20 mmol, 5 eq.) and the solution was
refluxed for 48 h. The reaction solution was cooled to ambient temperature, and the unreacted styrene was removed in vacuo. The product was isolated by silica column chromatography (1:2 ethyl acetate/hexanes) to yield a yellow oil (387 mg, 57%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.38-7.26 (m, 6H), 7.16-7.12 (m, 4H), 4.42-4.36 (m, 1H), 3.62-3.57 (t, $J$ = 7.2 Hz, 2H), 3.50-3.44 (d, $J$ = 16.0 Hz, 1H), 3.26 (s, 3H), 3.15-3.10 (d, $J$ = 16.0 Hz, 1H), 2.32-2.22 (m, 1H), 1.98-1.89 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 156.6, 149.6, 140.2, 124.9, 128.8, 128.5, 128.1, 128.0, 127.0, 126.0, 61.4, 43.0, 36.7, 35.9, 35.0.

4-(3-Bromophenyl)-2-methyl-6-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (11.4)

1,5-Dimethyl-3-(3-bromophenyl)-6-oxoverdazyl (1.50 g, 5.32 mmol) was dissolved in 10 mL of THF in a 25 mL round-bottom flask. Styrene (3.05 mL, 26.6 mmol, 5 eq.) and the solution was refluxed for 48 h. The reaction solution was cooled to ambient temperature, and the unreacted styrene was removed in vacuo. The product was isolated by silica column chromatography (1:2 ethyl acetate/hexanes) to yield a yellow oil (1.24 g, 61%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.54-7.52 (t, $J$ = 1.7 Hz, 1H), 7.44-7.41 (d, $J$ = 8.0 Hz, 1H), 7.36-7.32 (d, $J$ = 7.8 Hz, 1H), 7.21-7.15 (m, 3H), 7.12-7.07 (t, $J$ = 7.9 Hz, 1H), 6.95-6.90 (m, 2H), 7.69-7.64 (dd, $J$ = 8.7 Hz, 5.2 Hz, 1H), 4.33-4.26 (m, 1H), 3.72-3.64 (m, 1H), 3.21 (s, 3H), 2.62-2.52 (m, 1H), 2.27-2.17 (m, 1H); $^{13}$C
NMR (100 MHz, CDCl$_3$) $\delta$ 154.9, 145.8, 139.1, 133.7, 133.0, 130.3, 129.6, 128.3, 128.1, 127.3, 125.9, 122.1, 66.4, 45.0, 36.6, 33.3.

**1-Methyl-2-(3-nitrophenyl)-9-(methylcarboxylate)pyrazolo[1,5-d][1,2,4]triazinone (11.5)**

![Structure of 1-Methyl-2-(3-nitrophenyl)-9-(methylcarboxylate)pyrazolo[1,5-d][1,2,4]triazinone](image)

Compound 11.1 (1.00 g, 2.57 mmol) was heated neat at 150 °C for 2 days. The reaction solution was cooled to ambient temperature and the product was isolated by silica column chromatography (1:2 ethyl acetate/hexanes) to yield a white solid (524 mg, 62%). The unreacted starting material was recovered (231 mg, 23%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.06-9.04 (t, J = 2.0 Hz, 1H), 8.54-8.51 (d, J = 7.9 Hz, 1H), 8.43-8.39 (m, 2H), 7.77-7.72 (t, J = 8.1 Hz, 1H), 4.00 (s, 3H), 3.88 (s, 3H).

**3-Methyl-5-(pyridin-3-yl)-1,3,4-oxadiazol-2(3H)-one (11.6)**

![Structure of 3-Methyl-5-(pyridin-3-yl)-1,3,4-oxadiazol-2(3H)-one](image)

Compound 11.2 (200 mg, 0.651) was dissolved in 5 mL of THF in a 25 mL round-bottom flask equipped with a condenser. A 5 mL solution of 3 M HCl$_{aq}$ was added, and the reaction was
stirred and heated at 60 °C for 3 days. The reaction mixture was cooled to ambient temperature and extracted with 50 mL of dichloromethane 3 times. The dichloromethane extracts were combined, dried over sodium sulfate, and evaporated to give an oil. The pure product was isolated by silica gel column chromatography (1:2 ethyl acetate/hexanes) to yield a white solid (86 mg, 75%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 9.10-9.08 (d, J = 1.8 Hz, 1H), 8.76-8.73 (dd, J = 4.9 Hz, 1.5 Hz, 1H), 8.12-8.08 (dt, J = 8.0 Hz, 1.9 Hz, 1H), 7.45-7.41 (dd, J = 7.9 Hz, 5.0 Hz, 1H), 3.53 (s, 3H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) δ 153.2, 152.0, 150.9, 146.7, 132.6, 123.5, 120.2, 32.7.

2-Methyl-4-(4-nitrophenyl)-6-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (11.7)

1,5-Dimethyl-3-(4-nitrophenyl)-6-oxoverdazyl (530 mg, 2.14 mmol) was dissolved in 3 mL of THF in a 10 mL round-bottom flask. Styrene (1.23 mL, 10.7 mmol, 5 eq.) and the solution was refluxed for 48 h. The reaction solution was cooled to ambient temperature, and the unreacted styrene was removed in vacuo. The product was isolated by silica column chromatography (1:2 ethyl acetate/hexanes) to yield a yellow oil (478 mg, 64%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 8.08-8.04 (d, J = 9.0 Hz, 1H), 7.61-7.57 (d, J = 9.0 Hz, 1H), 7.21-7.12 (m, 3H), 6.93-6.89 (m, 2H), 4.70-4.65 (dd, J = 8.8 Hz, 5.6 Hz, 1H), 4.36-4.29 (m, 1H), 3.75-3.67 (m, 1H), 3.26 (s, 3H), 2.66-
2.56 (m, 1H), 2.29-2.20 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 154.7, 148.4, 144.8, 138.7, 137.9, 128.4, 128.3, 128.0, 127.4, 123.2, 66.8, 45.2, 36.8, 33.3.

3-Methyl-5-(4-nitrophenyl)-1,3,4-oxadiazol-2(3H)-one (11.8)

![Chemical Structure](image)

Compound **11.7** (200 mg, 0.570 mmol) was dissolved in 5 mL of THF in a 25 mL round-bottom flask equipped with a condenser. A 5 mL solution of 3 M HCl$_{aq}$ was added, and the reaction was stirred and heated at 60 °C for 3 days. The reaction mixture was cooled to ambient temperature and extracted with 50 mL of dichloromethane 3 times. The dichloromethane extracts were combined, dried over sodium sulfate, and evaporated to give an oil. The product was isolated by silica gel column chromatography (1:2 ethyl acetate/hexanes) to yield a white solid (81 mg, 72%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.36-8.32 (d, J = 9.0 Hz, 1H), 8.04-8.00 (d, J = 9.0 Hz, 1H), 3.56 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 153.0, 151.1, 149.2, 129.1, 126.3, 124.2, 32.9.

1-Methyl-2-(3-aminophenyl)-9-(methylcarboxylate)pyrazolo[1,5-d][1,2,4]triazinone (11.9)

![Chemical Structure](image)
Compound 11.5 (55 mg, 0.17 mmol) dissolved in 5 mL of ethanol in a 10 mL round-bottom flask. Sodium borohydride was added (13 mg, 0.34 mmol, 2 eq.) and stirred for one hour at ambient temperature after which the reaction mixture was quenched with 1 M HCl$_{\text{aq}}$ and extracted with 10 mL of dichloromethane 3 times. The dichloromethane extracts were combined, dried over sodium sulfate, and evaporated to give an oil. The pure product was isolated by silica gel column chromatography (1:1 ethyl acetate/hexanes) to yield a white solid (46 mg, 92%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.36 (s, 1H), 7.40-7.36 (d, 7.6 Hz, 1H), 7.34-7.28 (m, 2H), 6.88-6.84 (d, J = 7.9 Hz, 1H), 3.97 (s, 3H), 3.87 (s, 2H), 3.82 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 161.4, 151.7, 145.4, 138.3, 133.0, 129.2, 129.0, 119.5, 117.6, 115.6, 114.5, 52.3, 38.3.

1-Methyl-2-(3-benzamide(phenyl))-9-(methylcarboxylate)pyrazolo[1,5-d][1,2,4]triazinone (11.10)

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{CO}_2\text{Me} & \\
\text{N} & \quad \text{O} \\
\text{H} & \quad \text{Ac} & \text{Ph}
\end{align*}
\]

Compound 11.9 (40 mg, 0.13 mmol) was dissolved in 10 mL of DCM in a 25 mL round-bottom and cooled to 0 °C. Triethyl amine was added (39 mg, 54 µL, 0.39 mmol, 3 eq.) along with benzoyl chloride (36 mg, 30 µL, 0.26 mmol, 2 eq.) and stirred for 3 h, slowly warming to ambient temperature. The reaction mixture was extracted with 10 mL of dichloromethane 3 times. The dichloromethane extracts were combined, dried over sodium sulfate, and evaporated to give an oil. The product was isolated by silica gel column chromatography (1:2 ethyl acetate/hexanes).
to yield a white solid (41 mg, 76%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.43-8.39 (t, $J = 1.8$ Hz, 2H), 8.34 (s, 1H), 7.93-7.87 (m, 3H), 7.83-7.79 (d, $J = 7.9$ Hz, 1H), 7.56-7.50 (m, 2H), 7.49-7.42 (m, 2H), 3.95 (s, 3H), 3.80 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.9, 161.3, 151.7, 145.4, 138.2, 137.5, 134.5, 133.0, 131.8, 129.0, 128.9, 128.6, 127.0, 125.3, 122.7, 121.1, 114.6, 52.4, 38.4.

5-(3-Bromophenyl)-3-methyl-1,3,4-oxadiazol-2(3H)-one (11.11)

\[
\text{\text{N}} \quad \text{O} \\
\text{\text{N}} \quad \text{O} \\
\text{\text{Br}}
\]

Compound 11.4 (200 mg, 0.519 mmol) was dissolved in 5 mL of THF in a 25 mL round-bottom flask equipped with a condenser. A 5 mL solution of 3 M HCl$_{aq}$ was added, and the reaction was stirred and heated at 60 °C for 3 days. The reaction mixture was cooled to ambient temperature and extracted with 50 mL of dichloromethane 3 times. The dichloromethane extracts were combined, dried over sodium sulfate, and evaporated to give an oil. The product was isolated by silica gel column chromatography (1:2 ethyl acetate/hexanes) and recrystallized in 1:1 ethyl acetate/hexanes to yield a white crystals (86 mg, 75%): mp 73-76 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.99-7.97 (t, $J = 1.7$ Hz, 1H), 7.77-7.73 (dt, $J = 7.8$ Hz, 1.3 Hz, 1H), 7.65-7.61 (d, $J = 8.0$ Hz, 1H), 7.37-7.32 (t, $J = 7.9$ Hz, 1H), 3.51 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 153.3, 151.6, 134.3, 130.4, 128.3, 125.5, 123.9, 122.9, 32.7.

Dimethyl 4-(3-bromophenyl)-2-methyl-1-oxo-2,8-dihydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazine-6,7-dicarboxylate (11.12)
1,5-Dimethyl-3-(3-bromophenyl)-6-oxoverdazyl (1.60 g, 5.67 mmol) was dissolved in 5 mL of THF in a 25 mL round-bottom flask. Dimethyl acetylene dicarboxylate (4.03 g, 3.51 mL, 28.4 mmol, 5 eq.) was added and the solution was refluxed for 48 h. The reaction solution was cooled to ambient temperature and the unreacted DMAD was removed in vacuo. The product was isolated by silica column chromatography (1:2 ethyl acetate/hexanes) to yield a yellow solid (1.48 g, 62%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.50-7.47 (t, J = 1.7 Hz, 1H), 7.42-7.40 (d, J = 8.0 Hz, 1H), 7.35-7.31 (d, J = 7.8 Hz, 1H), 7.12-7.08 (t, J = 7.9 Hz, 1H), 4.83 (s, 2H), 3.75 (s, 3H), 3.43 (s, 3H), 3.35 (s, 3H).

1-Methyl-2-(3-bromophenyl)-9-(methylcarboxylate)pyrazolo[1,5-d][1,2,4]triazinone (11.13)

Compound 11.12 (500 mg, 1.18 mmol) was heated neat at 150 °C for 2 days. The reaction solution was cooled to ambient temperature and the product was isolated by silica column chromatography (1:2 ethyl acetate/hexanes) to yield a white solid (524 mg, 62%). The unreacted
starting material was recovered (231 mg, 23%); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.37 (s, 1H), 8.05-8.01 (d, J = 8.3 Hz, 2H), 8.56-8.53 (m, 2H), 3.98 (s, 3H), 3.84 (s, 3H).

4-(3-Fluoropyridin-4-yl)-2-methyl-6-phenyl-2,6,7,8-tetrahydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (11.14)

1,5-Dimethyl-3-(4-nitrophenyl)-6-oxoverdazyl (200 mg, 0.901) was dissolved in 1 mL of THF in a 10 mL round-bottom flask. Styrene (0.516 mL, 4.50 mmol, 5 eq.) and the solution was refluxed for 48 h. The reaction solution was cooled to ambient temperature, and the unreacted styrene was removed in vacuo. The product was isolated by silica column chromatography (1:2 ethyl acetate/hexanes) to yield a yellow oil (178 mg, 61%); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.34-8.32 (d, J = 1.7 Hz, 1H), 8.20-8.17 (d, J = 5.0 Hz, 1H), 7.19-7.12 (m, 3H), 7.05-7.02 (t, J = 5.4 Hz, 1H), 7.02-6.99 (m, 2H), 4.61-4.56 (t, J = 7.3 Hz, 1H), 4.07-4.00 (m, 1H), 3.80-3.72 (m, 1H), 3.29 (s, 3H), 2.60-2.50 (m, 1H), 2.22-2.09 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 157.2, 155.0, 154.6, 145.4-145.3 (d, J = 5.2 Hz), 141.93-141.91 (d, J = 1.8 Hz), 138.9, 138.6-138.5 (d, J = 17.8 Hz), 128.5, 128.2, 126.8, 123.8, 65.1, 44.4, 36.6, 34.1.

5-(3-Fluoropyridin-4-yl)-3-methyl-1,3,4-oxadiazol-2(3H)-one (11.15)
Compound **11.14** (100 mg, 0.308 mmol) was dissolved in 5 mL of THF in a 25 mL round-bottom flask equipped with a condenser. A 5 mL solution of 3 M HCl\textsubscript{aq} was added, and the reaction was stirred and heated at 60 °C for 3 days. The reaction mixture was cooled to ambient temperature and extracted with 50 mL of dichloromethane 3 times. The dichloromethane extracts were combined, dried over sodium sulfate, and evaporated to give an oil. The product was isolated by silica gel column chromatography (1:2 ethyl acetate/hexanes) to yield a white solid (111 mg, 67%); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 8.68-8.66 (d, \(J = 1.8\) Hz, 1H), 8.51-8.49 (d, \(J = 5.4\) Hz, 1H), 7.35-7.32 (t, \(J = 5.3\) Hz, 1H), 3.57 (s, 3H).

**3-Methyl-5-(4-aminophenyl)-1,3,4-oxadiazol-2(3H)-one (11.16)**

Compound **11.8** (60 mg, 0.27 mmol) was dissolved in 5 mL of ethanol in a 10 mL round-bottom flask. Sodium borohydride was added (20 mg, 0.54 mmol, 2 eq.) and stirred for one hour at ambient temperature afterwhich the reaction mixture was quenched with 1 M HCl\textsubscript{aq} and extracted with 10 mL of dichloromethane 3 times. The dichloromethane extracts were combined,
dried over sodium sulfate, and evaporated to give an oil. The product was isolated by silica gel column chromatography (1:1 ethyl acetate/hexanes) to yield a white solid (58 mg, 84%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.63-7.60 (d, J = 8.7 Hz, 1H), 6.71-6.67 (d, J = 8.7 Hz, 1H), 4.04 (br, 2H), 3.46 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 153.8, 153.6, 149.4, 127.2, 114.5, 113.3, 32.4.

7-Benzoyl-2-methyl-4-(4-nitrophenyl)-6-phenyl-2,8-dihydro-1H-pyrazolo[1,2-a][1,2,4,5]tetrazin-1-one (11.17)

![Chemical structure](image)

1,5-Dimethyl-3-(4-nitrophenyl)-6-oxoverdazyl (500 mg, 2.02 mmol) was dissolved in 3 mL of THF in a 10 mL round-bottom flask. Phenyl acetylene (1.03 g, 1.11 mL, 10.1 mmol, 5 eq.) and the solution was refluxed for 48 h. The reaction solution was cooled to ambient temperature, and the unreacted phenyl acetylene was removed \textit{in vacuo}. The product was isolated by silica column chromatography (1:2 ethyl acetate/hexanes) to yield a yellow oil (174 mg, 19%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.88-7.84 (d, J = 8.7 Hz, 2H), 7.52-7.48 (d, J = 8.8 Hz, 2H), 7.27-7.23 (d, J = 7.3Hz, 2H), 7.15-7.10 (t, J = 7.6 Hz, 1H), 6.99-6.94 (t, J = 7.9 Hz, 1H), 6.92-6.84 (m, 3H), 6.82-6.77 (t, J = 7.5 Hz, 2H), 5.12 (s, 2H), 3.55 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 190.1, 157.7, 149.0, 148.1, 140.6, 138.2, 136.1, 130.9, 130.2, 129.7, 128.1, 127.92, 127.86, 127.4, 126.4, 122.9, 112.2, 53.1, 37.8.

1-((4-Benzoyl-5-phenyl-1H-pyrazol-1-yl)(4-nitrophenyl)methylene)-3-methylurea (11.17)
Compound **11.16** (150 mg) was dissolved in 5 mL of toluene in a 10 mL round-bottom flask and refluxed for 48 h. The reaction solution was cooled to ambient temperature and the product was isolated by silica column chromatography (1:2 ethyl acetate/hexanes) to a yellow oil (18 mg, 12%); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.22 (s, 1H), 7.99-7.97 (d, $J = 9.1$ Hz, 2H), 7.80-7.76 (d, $J = 8.6$ Hz, 2H), 7.52-7.46 (t, $J = 7.6$ Hz, 1H), 7.39-7.33 (t, $J = 7.9$ Hz, 2H), 7.25-7.15 (m, 7H), 6.30-6.26 (q, $J = 4.1$ Hz, 1H), 3.21-3.18 (d, $J = 4.2$ Hz, 3H).

### 11.3 Results and Discussion

A subset of compounds was synthesized as part of a group effort with other members of the Georges lab for generating a library of compounds for testing against acute myeloid leukemia and multiple myeloma. Verdazyl radicals with functionalizable substituents on the 3-phenyl position **11.18** (Scheme 11-1) were prepared. These verdazyl radicals were reacted with styrene, DMAD and 2-benzoyl-1-phenylacetylene via the 1,3-dipolar cycloaddition reaction of the azomethine imine generated form the verdazyl radicals. The resultant cycloadduct compounds, termed 1$^{\text{st}}$ generation compounds, were subjected to their respective rearrangement inducing conditions to yield the 2$^{\text{nd}}$ generation compounds: oxadiazolones, pyrazolotriaziniones and pyrazoles. The general map of this synthetic strategy is shown in Scheme 11-1. In most cases, the 2$^{\text{nd}}$ generation compounds contained groups which could be used towards further derivatization. Nitro groups were reduced to amines and reacted with acid chlorides to afford
amide groups. Additionally, other functional groups present such as aryl bromides can be
derivatized using boronic acids via palladium coupling reactions and esters can be reacted with
amines to form amides. In total, 17 compounds were produced in this supplemental library,
however, due to the time constraint of one month spent on synthesis, not all planned compounds
were synthesized before being sent to The Princess Margaret Hospital for cancer cell line
screening.

**Scheme 11-1.** Synthetic map for DOS library starting with cycloaddition reactions then
rearrangements to product 2\textsuperscript{nd} generation compounds.
The compounds synthesized were tested for cytotoxicity in cell lines of acute myeloid leukemia and multiple myeloma at concentrations of 5000 µM and 500 µM. Of the compounds synthesized as part of this chapter, compound 11.10 was shown to kill both cell lines at the 5000 µM concentration. A more active compound, 11.19 made by Eric Chen (Figure 11-1), killed nearly all cells in both line at the lower 500 µM concentration.

![Chemical structures of compounds 11.10 and 11.19](image)

**Figure 11-1.** Active compounds as tested against acute myeloid leukemia and multiple myeloma cell lines.

Given the activity of compound 11.19, a dose response curve was made to explore the cytotoxic activity at even lower concentrations (Figure 11-2). Compound 11.19 showed activity at 250 µM. Though these results do not represent the activity associated with anti-cancer drugs, they do show potential for exploring verdazyl radical derived compounds as biological agents satisfying the aim of this project. Given the small sample size of 86 compounds in total tested and given that they were non-specific; two hits represent an encouraging result. Further work on optimizing these two compounds could lead to better specificity.
Figure 11-2. Dose response curve of compound 11.19 for acute myeloid leukemia and multiple myeloma cell lines.  

11.4 Summary

Verdazyl radicals have been recently shown to act successfully as substrates for the synthesis of a large variety of N-heterocycles. The diversity of possible scaffolds available from the common 1,5-dimethyl-3-phenyl-6-oxoverdazyl radical starting point bodes well with the concept of DOS to quickly generate a library of compounds with significant skeletal diversity. The viability of verdazyl radicals to generate a DOS library has been demonstrated and the products of this endeavour have been used to test for activity against two cancer cell lines. Of the 86 compounds tested, two showed activity with compound 11.19 seen to decrease the viability of both cancer cell lines at concentrations as low as 250 µM.
11.5 References


Chapter 12

12 Conclusion

12.1 Summary

The objective of this research was to explore the scope of and to obtain an understanding of the use of verdazyl radicals in the application of organic synthesis. The use of stable radicals as substrates for organic synthesis is an uncommon practice. The work demonstrated herein represents a unique approach to generating an increasing number of N-heterocycles accessible via verdazyl radical based chemistry. The breakthrough discovery of the disproportionation reaction of 1,5-dimethyl-3-phenyl-6-oxoverdazyl radical into a leucoverdazyl and an azomethine imine, a candidate for 1,3-dipolar cycloaddition reactions, opened up verdazyl radical based synthesis of N-heterocycles in the Georges lab.

Verdazyl radicals represent a structurally diverse family of stable radicals whose root structure is a 6-membered ring containing four nitrogen atoms. As discussed in chapter 1 of this thesis, reported examples include those with varying substituents at the 1,3,5 and 6-positions as well as inorganic examples containing phosphorus and boron in its backbone. This chemical family, rich in heteroatoms and structural diversity, holds great potential as a starting point for the synthesis of heterocycles. However this property of verdazyl radicals has only been explored thus far by the Georges lab.

Initially, the disproportionation of 6-oxoverdazyl radicals was used to demonstrate their use as precursors in 1,3-dipolar cycloaddition reactions in order to generate tetrahydropyrazolotetrazinones from alkene-based dipolarophiles. This work was extended to include alkynes as dipolarophiles, which resulted in the respective dihydropyrazolotetrazinone
cycloadducts as predicted. Interestingly, the alkyne-based dipolarophile work revealed an inherent instability of some of the cycloadducts to spontaneously rearrange after several days. Two distinct rearrangement reactions were observed with the alkyne cycloadducts: A rearrangement to form pyrazoles and a rearrangement to form pyrazolotriazinones in high yield upon heating. From here, research into rearrangement reactions of cycloadducts to second and third generation compounds was set in motion. Revisiting alkene-based dipolarophile cycloadducts in order to probe for rearrangement chemistry by reactions with acids, bases and nucleophiles, has led to new synthetic routes to oxadiazolones, tetrahydropyrazolotriazinones and triazoles. Verdzyl radicals were applied successfully to synthesizing macrocycles via tandem cycloadditions to form up to 21-membered rings.

In addition, a new synthesis for 1,5-dimethyl-6-oxoverdazyl radicals was developed out of necessity to move away from using methyl hydrazine as a starting material. Fortuitously, this new synthetic methodology allowed access to a increased number of alkyl substitutions on verdazyl radicals as well as the ability to synthesize unsymmetrical 1,5-dialkyl verdazyl radicals. These unsymmetrical examples were used to test the relative effects of certain alkyl substituents to the reactivity towards disproportionation of verdazyl radicals.

Chapter 10 of this thesis described an entry into verdazyl radical chemistry distinct from all of the previous work done in the Georges lab: triphenyl verdazyl radicals. In the case of triphenyl verdazyl radicals, direct radical addition onto electron-deficient alkynes provides a means to generating 1-(phenyl diazenyl)isoquinoline-3,4-dicarboxylates. The mechanism of this transformation was proposed to occur via a radical rearrangement reaction followed by a retro-Diels Alder fragmentation to yield the final product.
Lastly, a group effort was put forward to apply the chemistry developed thus far from verdazyl radicals in order to synthesize a small library of N-heterocycles of different scaffolds for use in testing for activity against cancer cell lines non-specifically. Of the 86 compounds tested, two showed some activity in killing cells lines of acute myeloid leukemia and multiple myeloma indicating potential use of verdazyl based chemistry in designing libraries of compounds for biological screening along the lines of DOS principles.

12.2 Future Work

Although much has been achieved in exploring the chemistry of verdazyl radicals in the Georges lab, study of these compounds is far from concluded. Ongoing work with applying enantioselectivity to the cycloaddition reactions is showing moderate success. Also, ongoing studies relating to the decarboxylations seen in some of our rearrangement reactions will shed light on the mechanistic aspects of this chemistry. Discussed below are potential areas where research into the chemistry of verdazyl radicals can be continued.

The entry into verdazyl radical chemistry via direct radical addition was only explored with a few examples of triphenyl verdazyl radicals. As mentioned in chapter 10, several interesting classes of fused heterocycles may be possible with the synthesis of 1,5-diphenyl-3-heteroverdazyl radicals using this chemistry. The means to synthesize these verdazyl radicals has not been reported and new synthetic methods for triphenyl verdazyl radicals needs to be developed to explore this potential avenue.

Other classes of verdazyl radicals such as phosphorus or boron containing examples have not been studied as precursors towards organic synthesis. These have potential to generate otherwise hard to obtain heterocycles if these heteroatoms can be successfully incorporated into any subsequent non-radical products by any developable chemistry. Indeed entirely different families
of stable radicals such as other hyrazyl-based radicals 12.1, nitroxides such as TEMPO 12.2 or thiazyl radicals 12.3 (Figure 12-1) could show analogous chemistry and act as precursors to 1,3-dipolar cycloaddition reactions or, like triphenyl verdazyl radicals, be used as substrates for synthesis by some other unique mechanism.

![Figure 12-1. Examples of other stable radicals](image)

As a more applied means of developing verdazyl radical chemistry, synthesis of a natural product that is otherwise difficult to make could fit well into the N-heterocyclic chemistry seen thus far. The rearrangements that have arisen from verdazyl radical-based chemistry are unique and thus, with an appropriate natural product could allow for showcasing our chemistry in the synthesis of a complex target.

In conclusion, with all the verdazyl radical chemistry developed there is enough material for a concise review paper which would summarize the findings of the past few years and appeal to a broader audience. Given the richness of the heteroatoms present in verdazyl radicals and their ability to undergo 1,3-dipolar cycloadditions to form 1st generation cycloadducts which can undergo unique rearrangements to produce 2nd and 3rd generation products, more research is necessary to bring out the full potential of using these stable radicals as substrates towards organic synthesis.