1-BENZOTRIAZOLYL-2-PROPYNONES AS NOVEL 1,3-BISELECTROPHILES, BENZOTRIAZOLE-ASSISTED THIOACYLATION AND SYNTHESIS OF ENERGETIC MATERIALS

By

JAMES WILLIAM ROGERS

A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

2006

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ACKNOWLEDGMENTS

I would like to foremost thank my wife, Yu Hong, for her companionship and guidance through my graduate career. There are many days that I might have failed in my resolve to complete my goals if it were not for her love and ability to brighten my spirits when it seemed there was no hope. I would also like to thank friends and some of the co-workers I have met along my graduate career, who have helped me in my personal life as well as my graduate life in chemistry: Dr. Rachel Witeck, Dr. Gary Cunningham, Dr. Chia Pooput, Dr. Yi'an Zhai, and Hui Tao. I would also like to thank my parents, William and Barbara Rogers, who always believed in and encouraged me to strive to be a better man, as well as my sister, Jeannine Rogers, for her friendship. I would like to thank all my other family members who gave me support and love throughout my life.

I am grateful for the help of Professor Alan Katritzky, whose great mind for novel chemistry guided the research in these pages. I would also like to thank my mentors of the past, most notably Professor Timothy Patrick, my research director at Southern Illinois University, where I received a Master of Science in chemistry. His belief in my abilities inspired me to continue my education at the University of Florida. There are many teachers and instructors I would like to thank over the years, all of whom have encouraged me and supported me to continue my stated goals.

I thank the Southern Illinois University at Edwardsville Chemistry Department for both my undergraduate and first two years of graduate study. The staff prepared me well for graduate school at the PhD level. Lastly, I thank the graduate department of the

University of Florida and the faculty of the Chemistry Department for accepting me, especially Professor James Deyrup, into their graduate program and for expanding my knowledge in chemistry greatly.

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Abstract of Dissertation Presented to the Graduate School
of the University of Florida in Partial Fulfillment of the
Requirements for the Degree of Doctor of Philosophy

1-BENZOTRIAZOLYL-2-PROPYNONES AS NOVEL 1,3-BISELECTROPHILES, BENZOTRIAZOLE-ASSISTED THIOACYLATION AND SYNTHESIS OF ENERGETIC MATERIALS

By

James William Rogers

May 2006

Chair: Alan R. Katritzky
Major Department: Chemistry

New synthetic strategies for the synthesis of several target molecules are the theme of this work. 1-Benzotriazolyl-2-propynones were shown to be novel 1,3-bis-electrophilic synthons. These synthons provided a new route in the synthesis of pyrido[1,2*a*]pyrimidin -2-ones, 2*H*-quinolizin-2-ones, pyrido[1,2-*a*]quinolin-3-ones, and thiazolo[3,2-*a*]-pyrimidin-7-ones. These new 1,3-bis-electrophilic synthons were compared with previous 1,3-bis-electrophilic methodologies from the literature and expanded on the role of these synthons by novel synthesis of new heterocyclic systems.

Aliphatic and aromatic thiocarbonyl-1H-6-nitrobenzotriazoles were synthesized (Chapter 3) as novel thioacylating reagents. To show their synthetic utility, these thiocarbonyl-1H-6-nitrobenzotriazoles were reacted with an alchohol to form the corresponding thionoesters.

Chapter 4 summarizes the work accomplished in collaboration with the US Army on the reasonable synthesis and characterization of broadly defined energetic materials.

CHAPTER 1
GENERAL INTRODUCTION

Syntheses of heterocyclic compounds possessing synthetic utility, biological activity and desirable physical properties are a constant area of interest for organic chemists, medicinal chemists and material scientists. Efficient methodologies for the synthesis of target molecules through the use of convenient starting materials, mild conditions and less laborious isolation and purification are highly sought after. This dissertation provides novel synthetic routes to fused heterocycles, thionoesters and energetic materials.

Versatile synthetic methodologies employing benzotriazole as a leaving group are covered in the first two chapters of this dissertation. Over the previous two decades, benzotriazole (Bt) has been used in countless synthetic processes including multistep preparations of drugs, preparation of biologically active compounds and synthetic analogs of natural products.[1] This is due to the multifaceted nature of benzotriazole and its unique electronic properties that enable it to act as an electron-donating or electron-withdrawing moiety, depending on the functional group attached to the benzotriazole nitrogen. Indeed, many applications of benzotriazole depend upon its leaving ability **1.1**, its ability to enhance α-proton acidity **1.2**, and its electron donor properties **1.3** (Figure 1-1). Generally, benzotriazole is considered to be comparable with cyano and phenylsulfonyl groups as a leaving group **1.1** or as an activator of α-CH proton loss **1.2**.[1] Benzotriazole also possesses electron donating characteristics **1.3** when there is an α-heteroatom on the carbon attached to nitrogen.

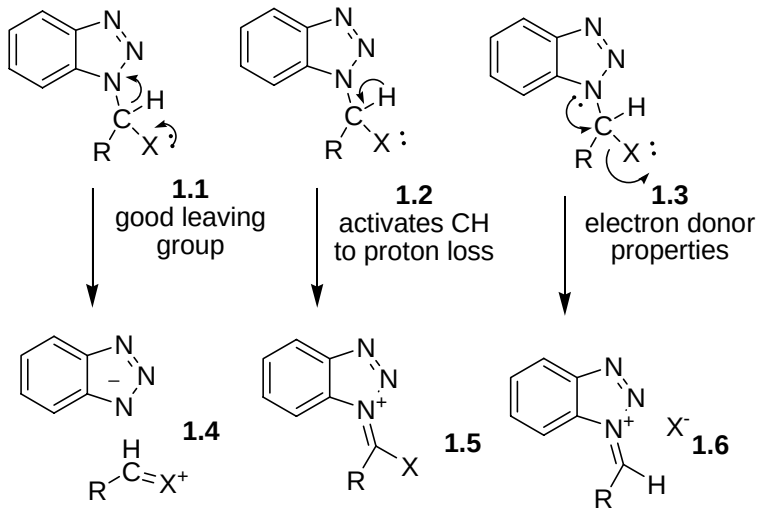


Figure 1-1. Electronic properties of benzotriazole.

Benzotriazole is an inexpensive and stable compound that is highly soluble in ethanol, benzene, toluene, chloroform, DMF and is slightly soluble in water.[2] It is also very soluble in basic solutions because of the acidity of the nitrogen hydrogen (pK_a of 8.2).[3] Benzotriazole is considered to be a useful synthetic auxiliary because it displays three important properties: i) it is readily removed at the end of a synthetic sequence (benzotriazole is especially advantageous because it can be recovered at the end of the reaction and reused), ii) it is easily introduced at the beginning of a reaction, and iii) lastly it is stable to various reaction conditions and can possibly activate other groups on the molecule.

Benzotriazole has been proven in hundreds of publications to be a good leaving group and can be efficiently removed at the end of a synthetic sequence by i) nucleophilic substitution **1.11** [4a-e] ii) elimination **1.12** [5a-e] iii) hydrolysis **1.10** [6a-e] and iv) ring scission[7] (Figure 1-2).

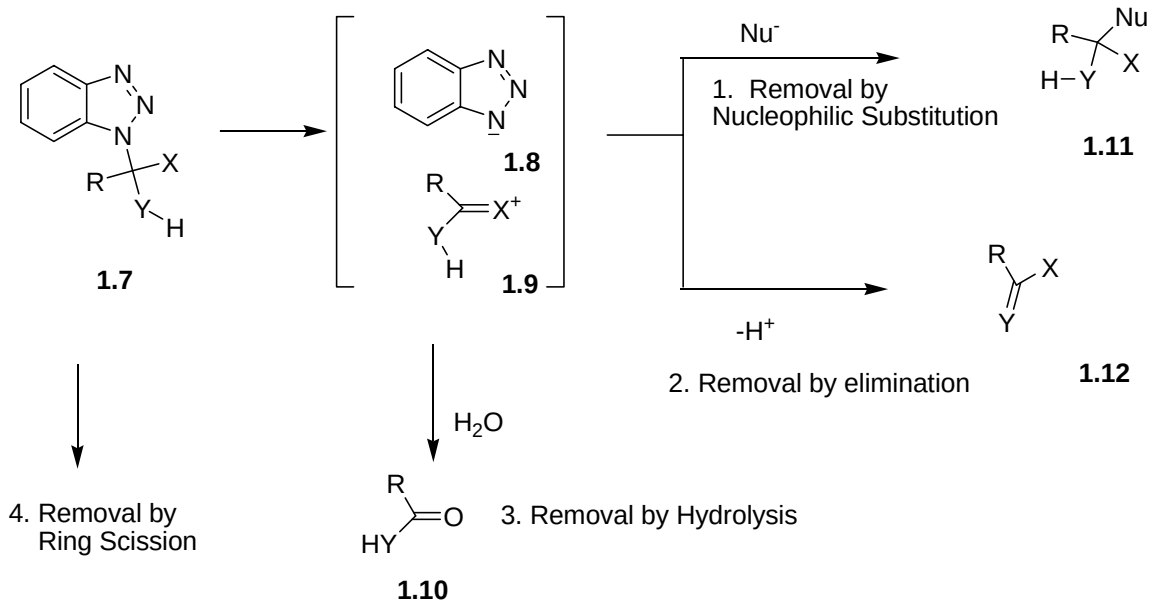


Figure 1-2. Methodologies for removal of benzotriazole.

The first three modes of removal all involve initial dissociation of benzotriazole into its anion **1.8** and formation of cation **1.9**. Dissociation is assisted by a suitable hetero-atom X and by a proton or Lewis acid catalyst which facilitates the departure of benzotriazole. The leaving ability of benzotriazole is also heavily influenced by the presence of other functional groups exemplified by group Y; for instance to remove benzotriazole by elimination, group Y must be connected to a hydrogen (Figure 1-2). Removal of benzotriazole by ring scission is different from the first three examples in that benzotriazole does not remain intact; instead its ring structure is cleaved. Probably the most well known example of ring scission on benzotriazole is the Graebe-Ulmann reaction in which carbazole **1.16** is formed from loss of N_2 from 1-phenylbenzotriazole **1.13**[7] (Figure 1-3). The reaction is thought to form a diradical intermediate **1.14a** or an iminocarbene intermediate **1.14b** which then undergoes cyclization to form (R)-4b*H*-carbazole **1.15** which isomerizes via hydrogen shift to carbazole **1.16**.

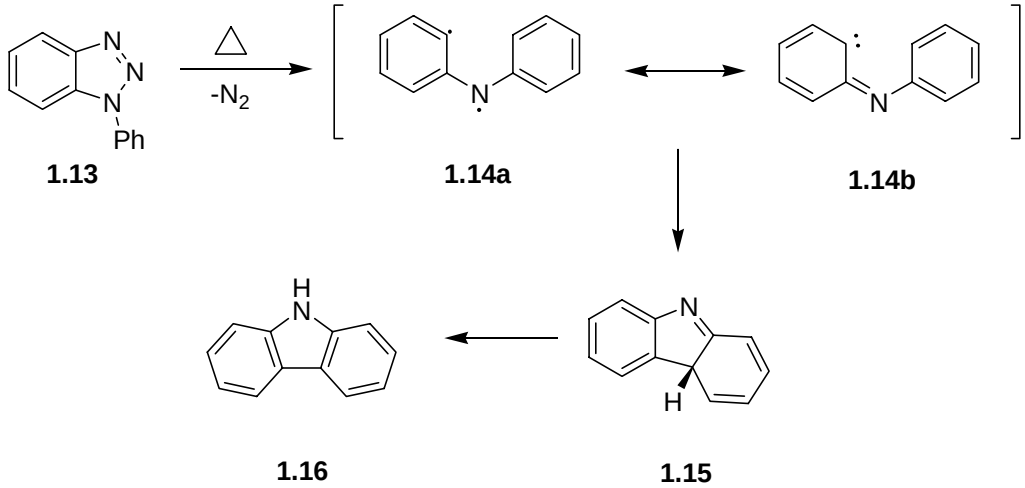


Figure 1-3. Graebe-Ulmann reaction.

A good synthetic auxiliary should be able to be inserted into the molecule of interest quite readily, and indeed benzotriazole has been successfully inserted in many diverse systems. Benzotriazole derivatives can be obtained through displacement of a halogen in i) alkyl,[8] or ii) acyl halides[9], iii) though displacement of hydroxyl groups in alcohols,[10] and by displacement of alkoxy groups in iv) acetals[11] or ketals.[12] Benzotriazole can also be inserted by addition to v) aldehydes[13] (including conjugate analogues), vi) imines,[14] vii) iminium salts,[15] and enamines[16] (Figure 1-4).

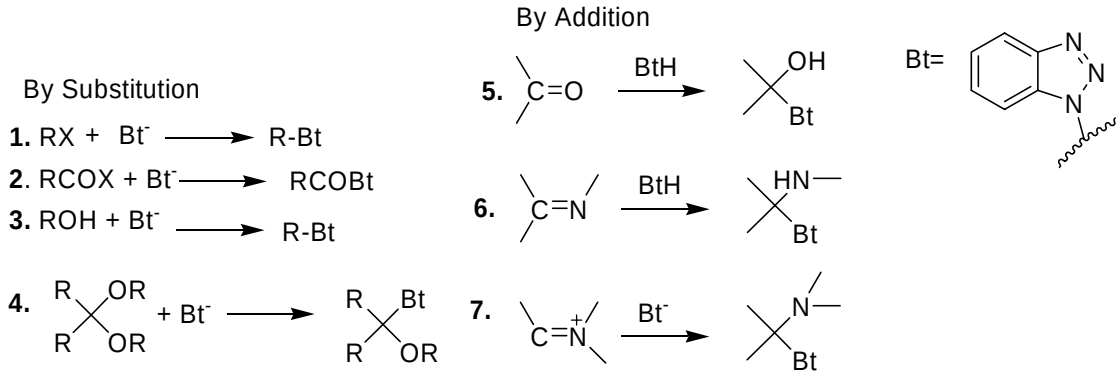


Figure 1-4. Insertion of benzotriazole.

As stated earlier in the introduction a useful synthetic auxiliary should be stable to various reaction conditions and possibly activate other groups on the molecule. There are several transformations from the literature in which benzotriazole does not leave and is

retained after the reaction. The most important of these transformations are i) deprotonation,[17] ii) substitution,[18] iii) addition,[19] iv) isomerization between 1- and 2-substituted benzotriazoles,[20] v) isomerization of benzotriazole within the molecule,[21] and vi) proton loss followed by rearrangement[22] (Figure 1-5).

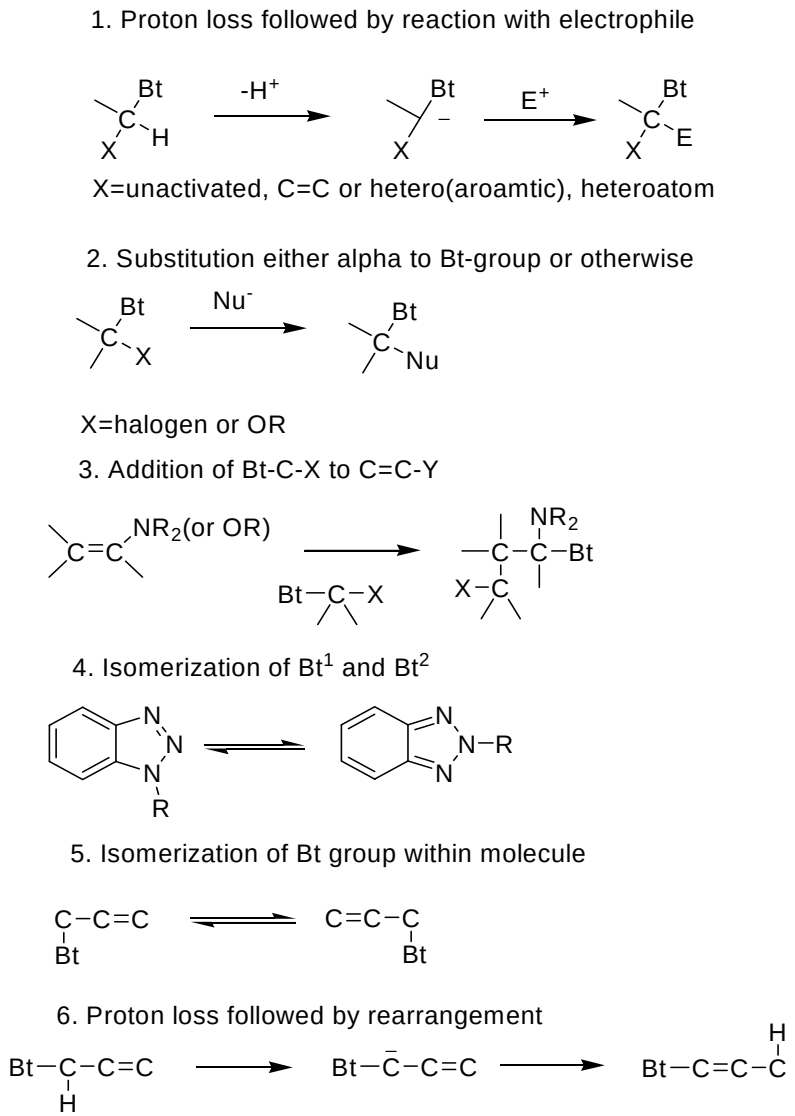
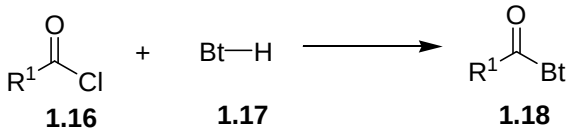


Figure 1-5. Transformations with benzotriazole.

Due to the unique electronic properties of benzotriazole the Katritzky group has developed numerous synthetic methodologies employing it as a synthetic auxiliary in the synthesis of countless heterocycles as well as other organic molecules. These reactions

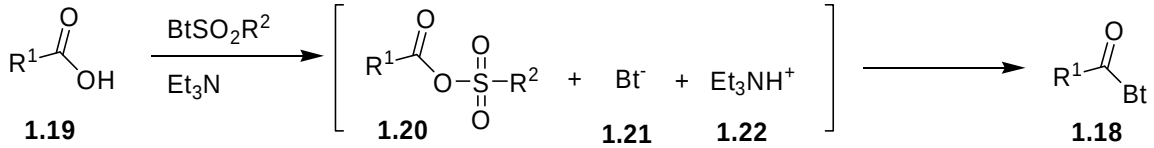
are typically shorter, offer higher conversion to product, and avoid the use of unstable or toxic chemical reagents such as acid chlorides.[1]

Over the last couple of years the Katritzky group has focused much of its attention on *N*-acylbenzotriazoles. Studies on *N*-acylazoles as acylating agents are nothing new; they have been studied since the 1960's by the Staab group.[23] *N*-Acylazoles have been typically synthesized from the corresponding acid chlorides **1.16** and *N*-acylbenzotriazoles **1.18** can also be synthesized in this manner[23] (Scheme 1-1).



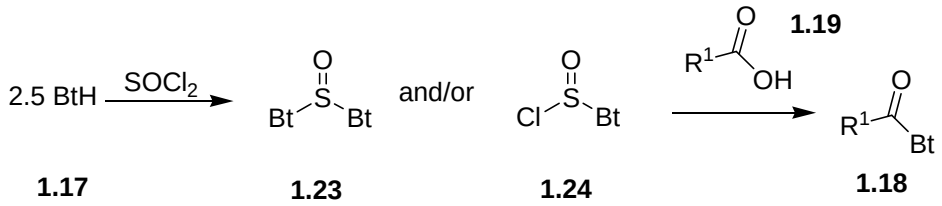
Scheme 1-1. *N*-Acylbenzotriazoles from acid chlorides.

Although the synthesis of *N*-acylazoles is routine, the requirement of their synthesis from acid chlorides is problematic and they can be both physiologically dangerous as well as unstable. Recently the Katritzky group discovered two new methodologies for the synthesis of *N*-acylbenzotriazoles that do not require the use of acid chlorides. The first methodology uses a sulfonylbenzotriazole as a counter attack reagent.[24, 25a] When a carboxylic acid **1.19** is exposed to a suitable base such as Et_3N the hydroxy group is deprotonated froming a carboxylate that can then undergo nucleophilic substitution with the electrophilic sulfonylbenzotriazole forming a mixed carboxylic sulfonic anhydride **1.20**. Benzotriazole anion **1.21** is then thought to counterattack the mixed carboxylic sulfonic anhydride intermediate **1.20** to form the corresponding *N*-acylbenzotriazole **1.18** (Scheme 1-2).



Scheme 1-2. *N*-Acylbenzotriazoles from sulfonylbenzotriazoles.

The Katritzky group later found that *N*-acylbenzotriazoles **1.18** could be synthesized by simply treating the carboxylic acid **1.19** in the presence of thionyl chloride and excess benzotriazole **1.17**[26] (Scheme 1-3). This methodology is often more advantageous than synthesizing *N*-acylbenzotriazoles from the previous route (Scheme 1-2) since thionyl chloride and benzotriazole are commercially available while sulfonyl-benzotriazole has to be prepared in a separate step.

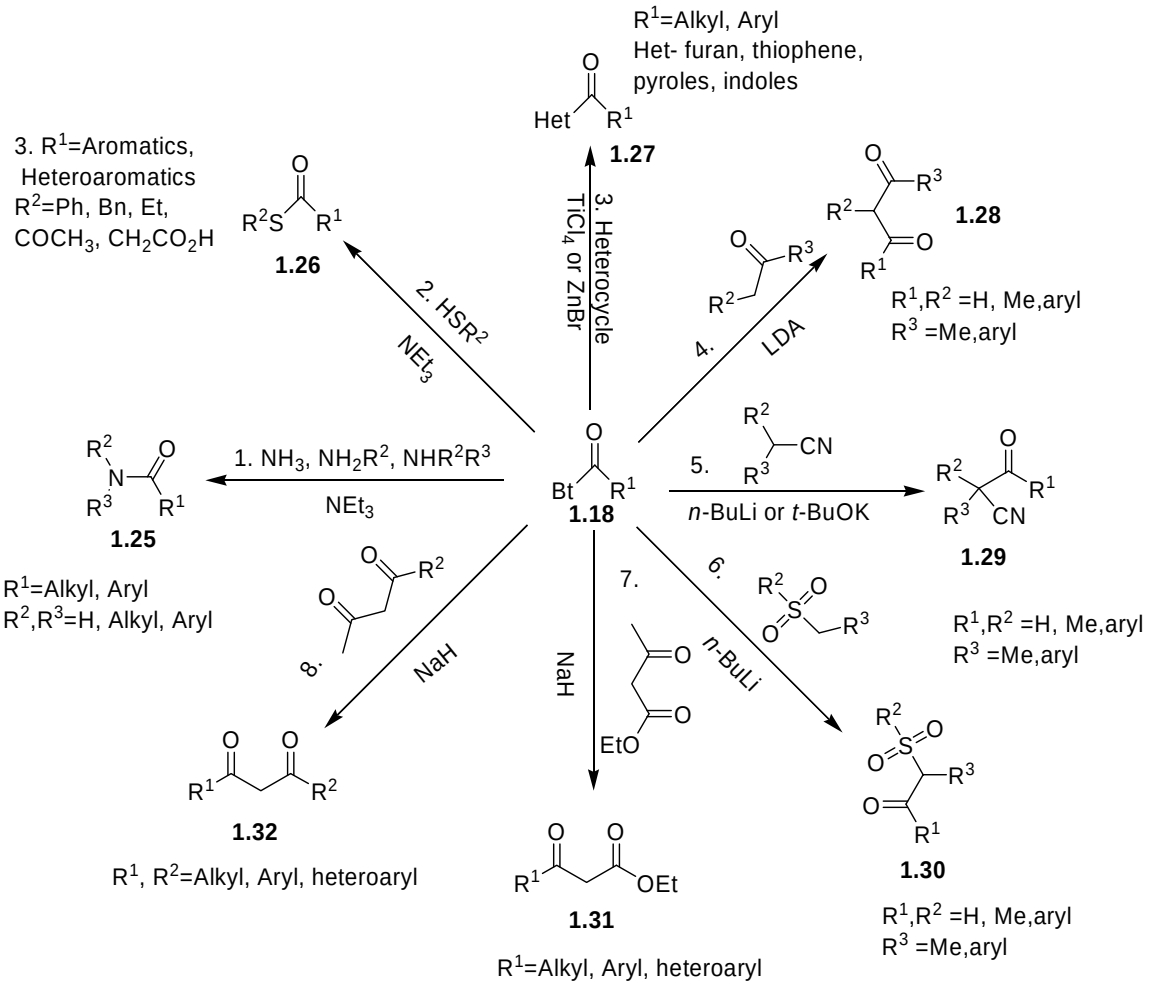


Scheme 1-3. *N*-Acylbenzotriazoles from carboxylic acids and thionyl chloride.

A wide range of *N*-acylbenzotriazoles have been synthesized through these two different methodologies, including alkyl, aryl, heterocyclic, unsaturated, and other functionally substituted derivatives.[24,26] There are several acid chlorides with the same functionalities as the synthesized *N*-acylbenzotriazoles that are unstable, difficult to prepare or in some cases unknown.[27]

Reactions with *N*-acylbenzotriazoles have been extensively studied by the Katritzky group over the past 5 years. *N*-Acylbenzotriazoles have been found to undergo N-,C- and S-acylation with the following reagents: i) amines (ammonia, primary and secondary) to form amides,[25a] ii) thiols to form thiol esters,[28] iii) heterocycles under Friedel-Crafts reaction conditions to form C-acylated heterocycles,[29] C-acylated with iv) (a) ketones,[25e] (b) cyanides[30] and (c) sulfones[31] to form β-diketones, β-ketonitriles and β-

ketosulfones respectfully, v) ethyl acetoacetate to form β-ketoesters and vi) α-acetylketones to form complex β-diketones[32] (Scheme 1-4).



Scheme 1-4. N-,C- and S-Acylation of *N*-acylbenzotriazole.

N-Acylbenzotriazoles have been successfully acylated using a variety of nucleophiles and the yields have been comparable to other methods which mainly used acid chlorides as the acylating reagent.[27] *N*-Acylbenzotriazoles offer advantages over the corresponding acid chlorides in their stability towards hydrolysis, their chemo-selectivity and crystallinity. It should be noted that they are especially advantageous when acid chlorides are unknown, difficult to prepare, handle and/or store. For these reasons the Katritzky group has expanded the research on *N*-acylbenzotriazoles and created

numerous examples of derivatives that have been successfully acylated with several types of nucleophiles.

In Chapter 2 1-benzotriazolyl-2-propynones are shown to be very interesting *N*-acylbenzotriazoles because they behave as 1,3-bis-electrophiles. 1-Benzotriazolyl-2-propynones undergo cyclization with 1,3-bis-nucleophiles to form various α-unsaturated cyclic ketones through the following mechanism (Figure 1-6).

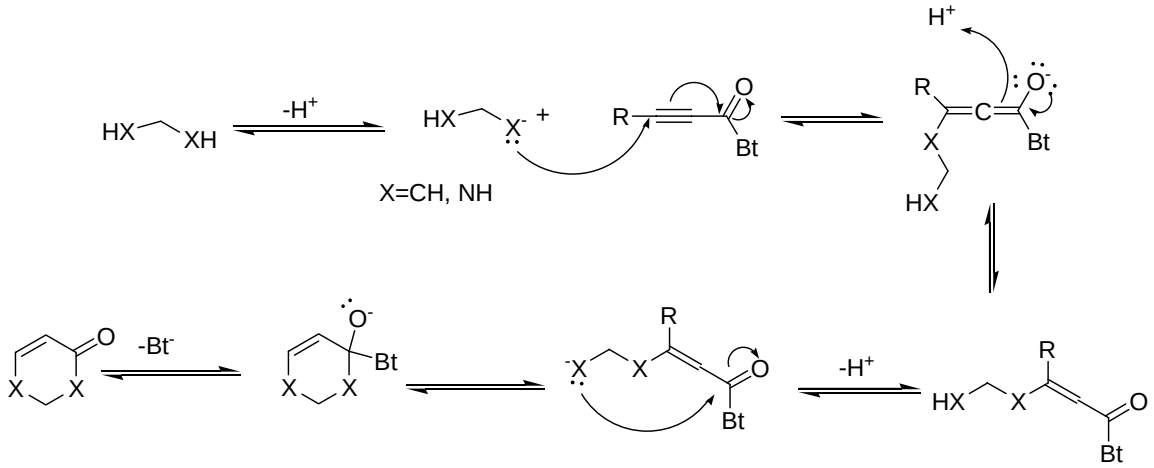
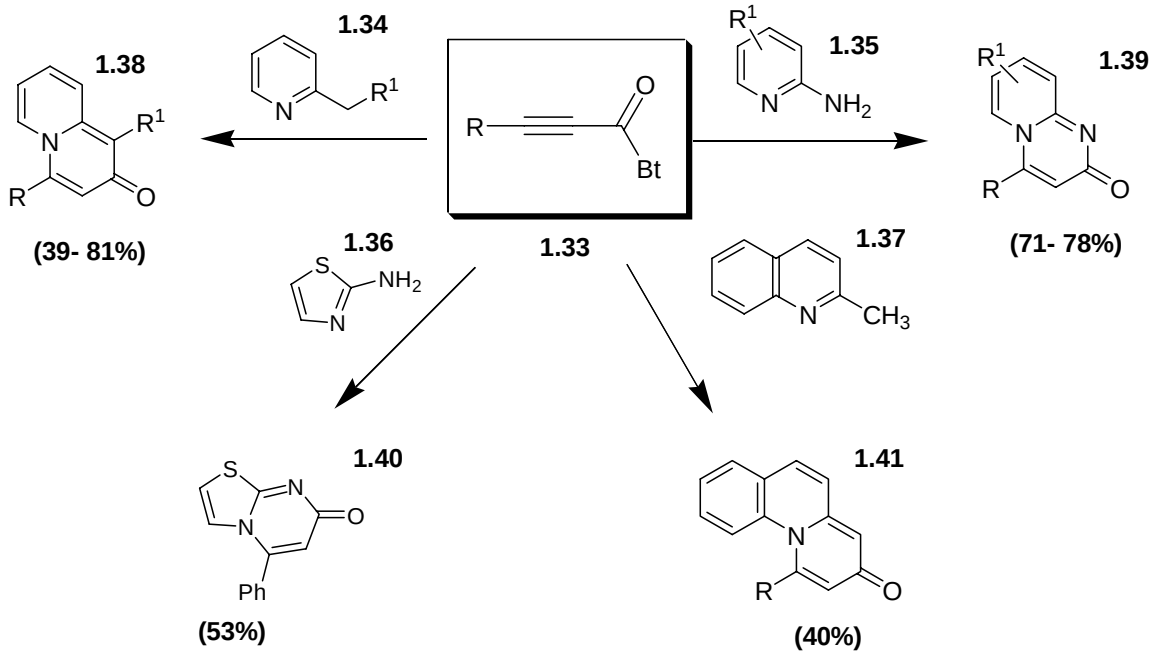


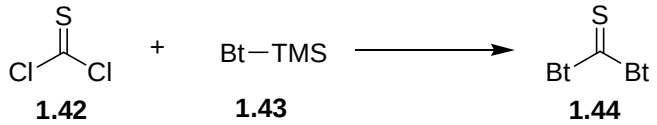
Figure 1-6. Cyclization mechanism for 1-benzotriazolyl-2-propynone.

1-Benzotriazolyl-2-propynones **1.33** (Chapter 2) were reacted with 2-amino-pyridines **1.35**, 2-picolines **1.34**, 2-methylquinoline **1.37** and 2-aminothiazole **1.36** to form pyrido[1,2-*a*]pyrimidin-2-ones **1.39**, 2*H*-quinolizin-2-ones **1.38**, pyrido[1,2-*a*]quinolin-3-ones **1.41**, and thiazolo[3,2-*a*]pyrimidin-7-ones **1.40** in moderate to excellent yields (Scheme 1-5).

Successful applications of *N*-acylbenzotriazoles as novel acylating reagents have also prompted investigation into a second area of study (chapter 3): the use of bis-(benzotriazolyl)methanethione as a mild thioacylating reagent.[33] Bis-(benzotriazolyl)-methanethione **1.44** is easily prepared from 1-trimethylsilylbenzotriazole **1.43** and thiophosgene **1.42** in quantitative yield[34] (Scheme 1-6).

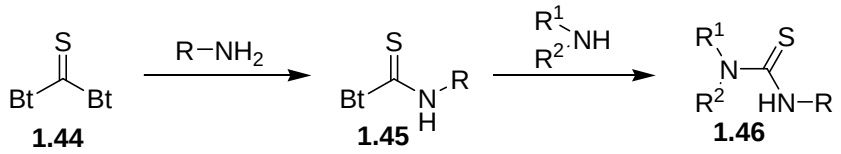


Scheme 1-5. Cyclization reactions of 1-benzotriazolyl-2-propynones.



Scheme 1-6. Synthesis of bis-(benzotriazolyl)methanethione **1.44**.

There was only one example from the literature before 2003 in which bis-(benzotriazolyl)-methanethione was reacted with an amine (aniline) to form a thiourea (diphenyl-thiourea).[34] The Katritzky group greatly expanded the work for the preparation of unsymmetrical di- and trisubstituted thioureas using compound **1.44** as a thiophosgene equivalent. First bis-(benzotriazolyl)methanethione **1.44** was reacted with one equivalent of a primary amine to form 1-(alkyl/arylthiocarbamoyl)-benzotriazoles **1.45** in near quantitative yields (Scheme 1-7). Then compound **1.45** was further reacted with either a primary or secondary amine to form unsymmetrical di- and trisubstituted thioureas **1.46**.

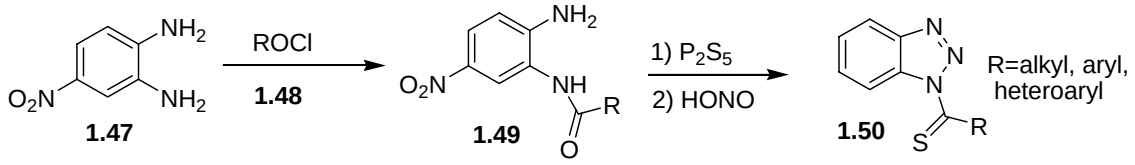


Scheme 1-7. Synthesis of unsymmetrical di- and trisubstituted thioureas **1.46.**

It was found by Katritzky et al. that the thiocarbamoylbenzotriazoles **1.45** synthesized were stable at room temperature for several weeks. Thiocarbamoyl-benzotriazoles **1.45** are masked isothiocyanates and are superior to them because they are more stable and their reactions with amines are faster, higher-yielding and less laborious in isolation and purification.[33]

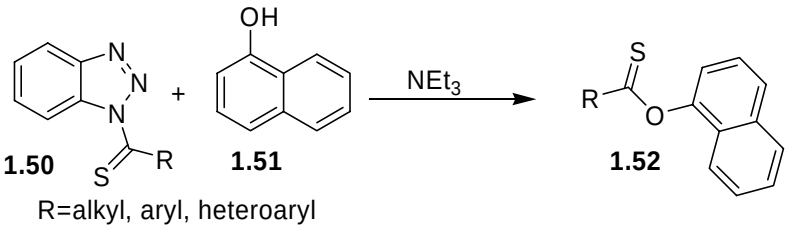
Chapter 3 of this dissertation expands upon the previous work on thiocarbamoyl-benzotriazoles **1.45** by preparing a broad range of reagents for thioacylation, namely thioacyl nitrobenzotriazoles **1.50**.[35] A previous route established by the Rapoport group was used to synthesize aliphatic, aromatic and heterocyclic substituted derivatives.[36a,b]

Treatment of 4-nitrobenzene-1,2-diamine **1.47** with the corresponding acid chlorides **1.48** gave regioselectively the intermediate amides **1.49**, which were then converted to the corresponding thioamides by phosphoruspentasulfide and then cyclized by treatment with sodium nitrate in acetic acid to yield the corresponding thioacyl nitrobenzotriazoles **1.50** (Scheme 1-8).



Scheme 1-8. Synthesis of thioacyl nitrobenzotriazoles **1.50.**

It was found that all thioacyl nitrobenzotriazoles **1.50** were stable at room temperature for several weeks and they readily reacted with 1-naphthalenol **1.51** to produce thionoesters **1.52** in good to almost quantitative yield (Scheme 1-9).



Scheme 1-9. Synthesis of thionoesters **1.52**

As part of a collaborative project with the US Army on development of energetic materials (Chapter 4), synthesis of three different types of energetic materials was accomplished (blowing agents, hypergolic agents and dinitrosubstituted five membered heterocycles).

Blowing agents are very well known as explosive formulations but they are not only limited to this role; for instance, dinitropentamethylenetetramine (DNPT) and *p*-tolylsulfonylhydrazine (PTS) are employed in the production of microcellular rubber.[37] Some blowing agents such as azodicarbonamide (ADCA) are used in the plastics industry to provide polymer films.[38-40] Blowing agents are also useful additives in propellant formulations.[41-43]

The US Army employs trinitrotoluene (TNT) and cyclotrimethylenetrinitramine (RDX) formulations as explosives. Blowing agents included in these formulations ideally should display separate isotherms from the other components of the explosive mixture. Addition of these blowing agents in explosive formulations provides a means to temper the cook off violence of the explosion. The following compounds were synthesized as potential blowing agent candidates from methodologies which could be easily scaled-up (Figure 1-7). The evaluation of the thermal properties of these compounds is included in chapter 4.

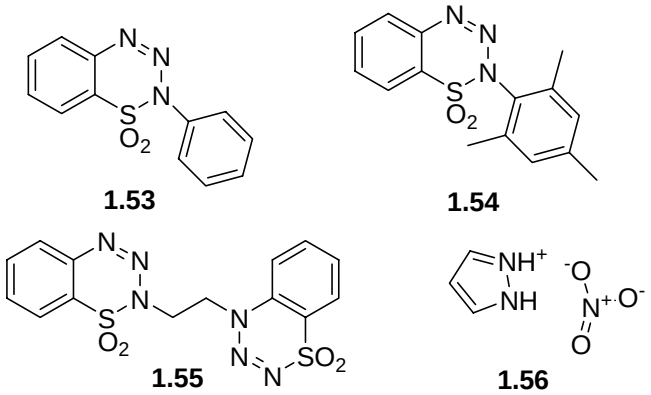


Figure 1-7. Blowing agents.

Hypergolic agents are compounds that can be used as fuels and oxidizers which ignite on contact with one another and therefore do not need a source of ignition.[44]

Hypergolic propellants have advantages over other propellants such as cryogenics in that they are easily stored and are relatively inert until they are in contact with the other agent. Since hypergolic propellants do not need an ignition source, they are often the propellant of choice for spacecraft and satellites as they are required to stop and start their engines thousands of times over the design life of the vehicle, thereby eliminating one source of possible failure.[45] Synthesis of the following hypergolic fuels was requested by the US Army that could potentially be scaled-up to provide 50-100 g quantities (Figure 1-8).

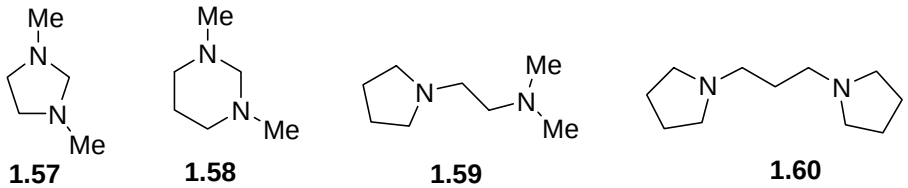
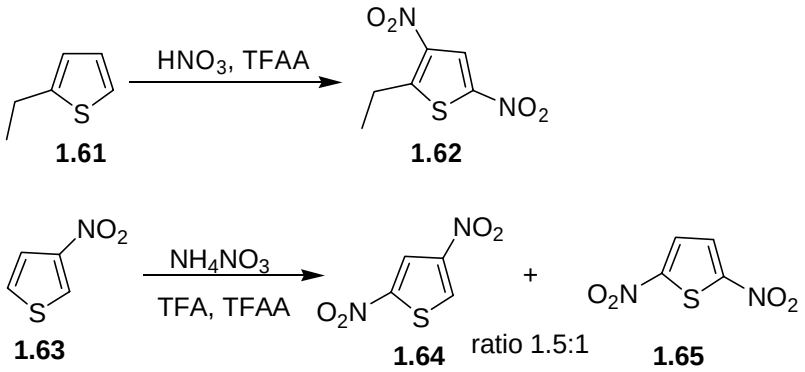


Figure 1-8. Hypergolic fuels.

Dinitro derivatives of five-membered heterocycles may be of interest as energetic materials and/or possible blowing agent candidates. They have also been shown to have diverse biological activity; for instance 2,4-dinitroimidazole derivatives have been shown

to be very effective agents in increasing the sensitivity of hypoxic cells toward irradiation in cancer radiotherapy.[46] Numerous dinitro heterocycles have also been shown to be useful intermediates; for instance Padwa and Watterson recently converted dinitro furan into various polysubstituted phenols through S_nAr nucleophilic substitution reactions.[47] Two dinitro heterocyclic derivatives **1.62**, **1.64, 1.65** (dinitrothiophenes isolated as a mixture of isomers) were successfully synthesized in moderate to excellent yield with more examples planned for future work (Scheme 1-10).



Scheme 1-10. Synthesis of dinitrothiophenes.

In summary, an efficient synthesis of three types of energetic materials was developed. The previously unreported decomposition profiles for three blowing agent candidates were analyzed by thermal analysis for evaluation as possible munitions additives. The fourth blowing agent candidate's **1.56** decomposition profile was analyzed by TG_A and DSC. Also, several novel fused heterocyclic derivatives were synthesized by reacting 1,3-bisnucleophiles with 1-benzotriazolyl-2-propynones. Finally, thioacyl nitrobenzotriazoles were shown to be effective thioacylating reagents and are a viable alternative to previous problematic routes.

CHAPTER 2
1-BENZOTRIAZOLYL-2-PROPYNONES AS NOVEL 1,3-BISELECTROPHILIC SYNTHONS

2.1 Introduction

As a structural motif pyrido[1,2-*a*]pyrimidines have shown very diverse biological activities,[48] for this reason these compounds have become interesting synthetic targets over the previous years. Their structural motif can be seen below in the tranquilizer pirenperone,[49a] the antiallergic agent ramastine,[49b] an antiulcerative agent,[49c] and an antiasthmatic agent[49d] (Figure 2-1).

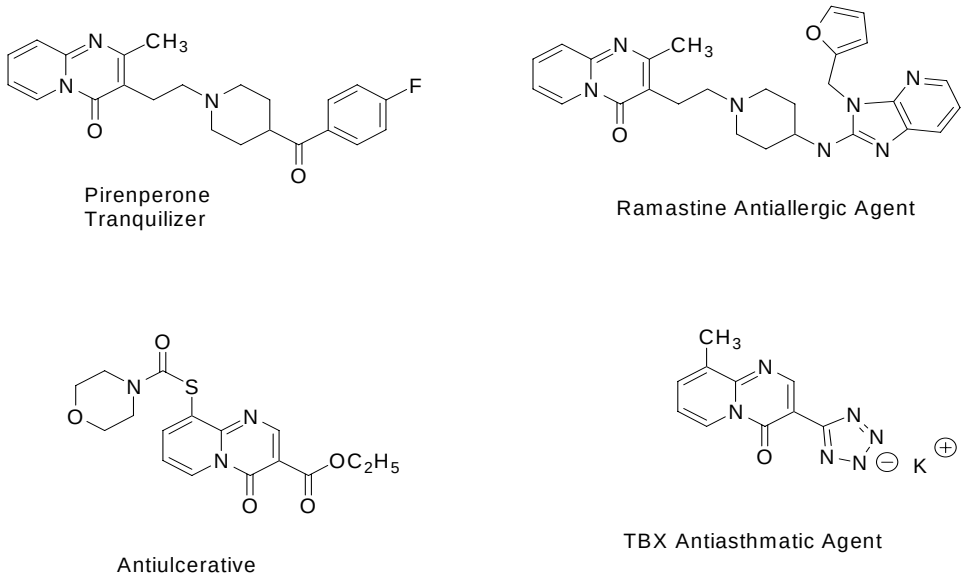
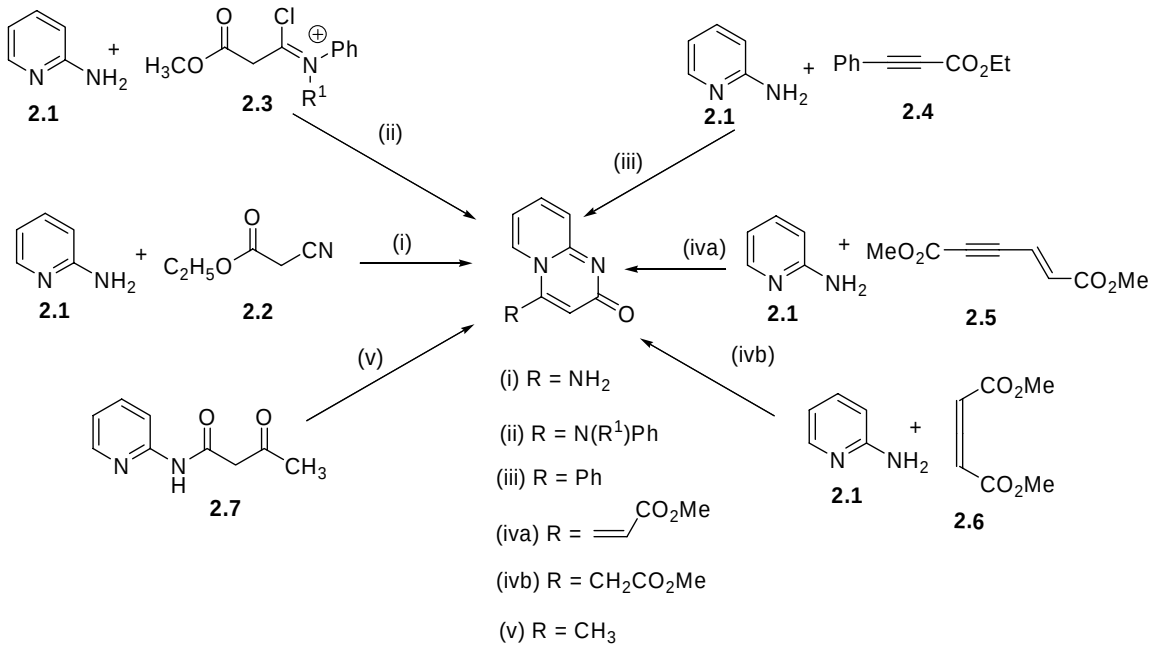


Figure 2-1. Pyrido[1,2-*a*]pyrimidines possessing diverse biological activities.

All the examples from Figure 1 are pyrido[1,2-*a*]pyrimidin-4-ones which are the most studied class due to their biological activity. Due to the interests these compounds have generated numerous synthetic routes are available for their synthesis.[50] In comparison, pyrido[1,2-*a*]pyrimidin-2-ones are a less studied class although there are

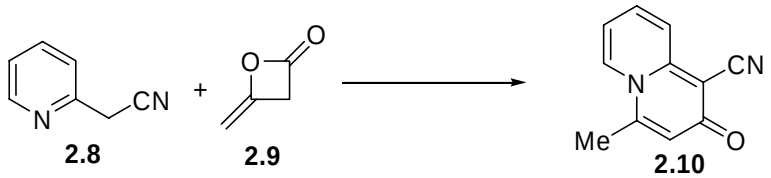
several literature methods that were found (Scheme 1-1) for their synthesis: i) cyclization of 2-aminopyridine **2.1** with ethyl cyanoacetate **2.2** at 80–100 °C and 14 kbar;[51] ii) the cyclization of 2-aminopyridine with the Vilsmeier-Haack **2.3** reagent prepared in situ from *N*-alkyl-*N*-arylethoxycarbonylacetamide and phosphorus oxychloride, which always affords a mixture of the pyrido[1,2-*a*]pyrimidin-2-ones and pyrido[1,2-*a*]pyrimidin-4-ones;[52] iii) reaction of phenylpropiolic ester **2.4** with 2-aminopyridine, which forms a significant amount of undesired side products;[53,48] (iv) reaction of dimethyl hex-2-en-4-yne-1,6-dioate **2.5**[54] or allene-1,3-dicarboxylic esters **2.6**[55] with 2-aminopyridines; and v) acid catalyzed cyclization of *N*-acetoacetylated 2-amino pyridines/picolines/quinolines **2.7** under microwave assisted synthesis.[56]



Scheme 2-1. Literature methods for synthesis of pyrido[1,2-*a*]pyrimidin-2-ones.

Surprisingly compared to pyrido [1,2-*a*]pyrimidin-2-ones quinolizin-2-ones are of a sparsely studied class of compounds; there is only one reported synthetic procedure. Only one quinolizin-2-one derivative was found from the literature, 4-methyl-2-oxo-2*H*-quinolizine-1-carbonitrile **2.10** which is formed by the reaction of 2-pyridylacetonitrile

2.8 with 4-methyleneoxetan-2-one **2.9** (Scheme 2-2).[57] There were no reported examples from the literature that used picolines in the place of 2-aminopyridines in the reaction with acetylenic carboxylic acid derivatives to form the corresponding quinolizin-2-ones.

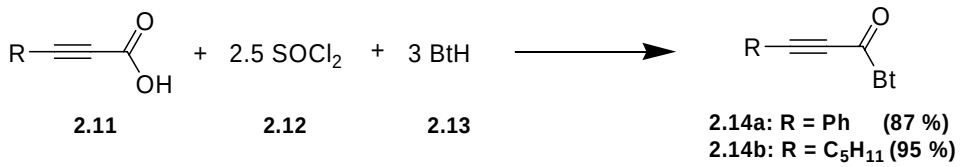


Scheme 2-2**.** 2-Pyridylacetonitrile with 4-methyleneoxetan-2-one.

There are numerous examples in the literature which employ *N*-acylbenzotriazoles as mild and neutral *N*-acylating agents. Some examples include the preparation of primary, secondary, and tertiary amides[25a] including formylation[25b] and trifluoroacylation.[25c] *N*-Acylbenzotriazoles are used for regioselective *C*-acylation of ketone enolates into α-diketones[25e] and are also used for the *O*-acylation of aldehydes.[25d] The Katritzky group has an efficient method for the synthesis of *N*-acylbenzotriazoles from acetylenic-carboxylic acids.[26] 1-Benzotriazolyl-2-propynones are formed from the reaction of acetylenic-carboxylic acids and thionyl chloride and benzotriazole. These compounds are 1,3-bis-electrophiles and their reaction with 2-aminopyridines leads to an improved syntheses of pyrido[1,2-*a*]pyrimidin-2-ones.

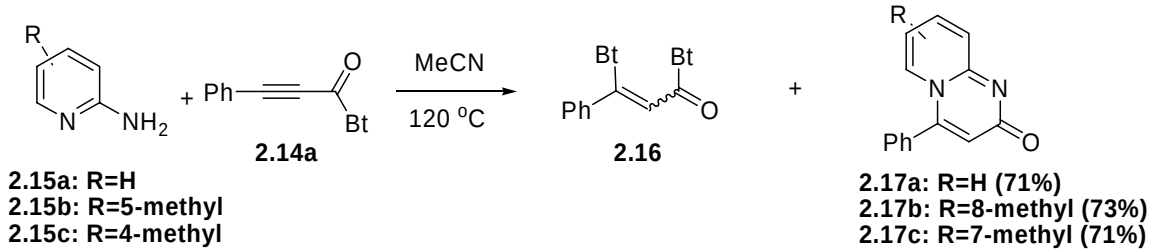
2.2 Results and Discussion

Two examples of alkyl and aryl substituted 1-benzotriazolyl-2-propynones were synthesized, 1-benzotriazol-1-yl-3-phenylpropynone and 1-benzotriazol-1-yl-oct-2-yn-1-one **2.14a,b** which were prepared in 87% and 95% yield (Scheme 2-3). 1-Benzotriazol-1-yl-3-phenylpropynone **2.14a** was previously reported by our group[26]; 1-benzotriazol-1-yl-oct-2-yn-1-one **2.14b** is a novel compound.



Scheme 2-3**.** Synthesis of substituted 1-benzotriazolyl-2-propynones.

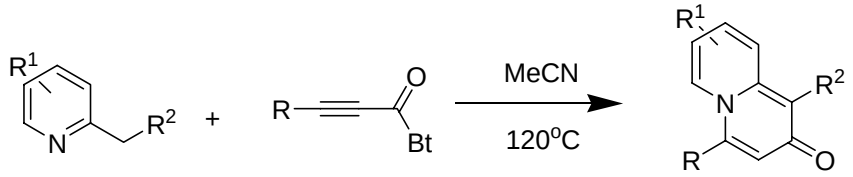
The first attempted synthesis of pyrido[1,2-*a*]pyrimidine-2-one **2.17a** (conducted at 80–100 ^{o}C in acetonitrile for 2–4h in a sealed tube), found that a significant amount of byproduct **2.16** was obtained along with the desired product **2.17a**. In order to isolate the byproduct 1-benzotriazol-1-yl-3-phenylpropynone, compound **2.14a** and 2-amino-pyridine **2.15a** were reacted at a lower temperature 80 ^{o}C with refluxing and in less time (2 hr), compound **2.17a** was isolated in 27% yield along with the by-product **2.16** in 46% yield (Scheme 2-4). The by-product **2.16** is probably formed by the counter attack of benzotriazole anion with 1-benzotriazol-1-yl-3-phenylpropynone **2.14a**. It was found that byproduct **2.16** formation was significantly decreased by conducting the reaction under harsher conditions using a sealed tube at 120 ^{o}C for 12 hours allowing clean conversion to the pyridopyrimidine **2.17a** (R = Ph) in 71 % yield after column purification (Scheme 2-4). Use of 4- and 5-methyl substituted 2-aminopyridines also resulted in the formation of corresponding pyridopyrimidines **2.17b** and **2.17c** in yields of 73% and 71%.



Scheme 2-4. Reaction of 1-benzotriazol-1-yl-3-phenylpropynone and 2-aminopyridines.

Synthesis of 2*H*-quinolizin-2-ones was performed by reacting 2-picoline with 1-benzotriazol-1-yl-3-phenylpropynone **2.14a** in a sealed tube at 120 ^{o}C in acetonitrile for 12 hours. This afforded the expected quinolizin-2-one **2.19a** in 61% yield (Scheme 2-5).

Similarly, reactions of 1-benzotriazol-1-yl-3-phenylpropynone **2.14a** and 1-benzotriazol-1-yl-oct-2-yn-1-one **2.14b** with 2-picoline derivatives afforded the corresponding 2*H*-quinolizin-2-ones **2.19b-f** in moderate to good yields.



2.18 **2.14a,b** **2.19**

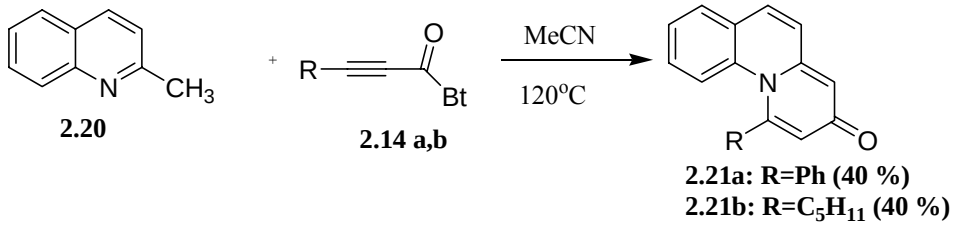
Scheme 2-5**.** Reaction of 2-picolines and 1-benzotriazolyl-2-propynones.

2.19	R	R^1	R^2	Yield (%)
a	Ph	H	H	61
b	Ph	H	CN	81
c	Ph	H	Ph	50
d	Ph	H	Me	51
e	C_5H_{11}	H	H	39
f	Ph	9-methyl	H	53

Surprisingly few reports were found in the literature on reactions of propionates and 2-picoline or its derivatives leading to the formation of fused ring systems. The reaction of 2-methylpyridine-1-oxide with methyl-3-phenyl-2-propanoate to give methyl-2-(2-methyl-3-pyridyl)-3-oxo-3-phenyl)propanoate is the only known analogue.[58] 1-Benzotriazolyl-2-propynones **2.14a,b** react easily as 1,3-bis-electrophilic synthons to give fused ring products, since they are very good acylating reagents.

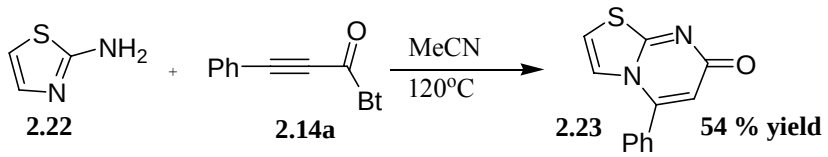
The *N*-acylbenzotriazole methodology, developed for the preparation of pyrido[1,2-*a*]pyrimidin-2-ones and 2*H*-quinolizin-2-ones, has also been extended to provide access to the fused ring systems of pyrido[1,2-*a*]quinolin-3-ones and thiazolo[3,2-*a*]pyrimidin-7-ones. Reactions of 2-methylquinoline **2.20** with 1-benzotriazol-1-yl-3-phenylpropynone **2.14a** or 1-benzotriazol-1-yl-oct-2-yn-1-one **2.14b** in a sealed tube at 120 °C in

acetonitrile afforded the expected 1-phenyl- and 1-pentylpyrido[1,2-*a*]quinolin-3-ones **2.21a,b** in 40% yields (Scheme 2-6).



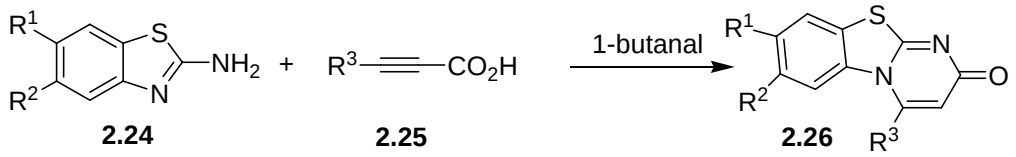
Scheme 2-6**.** Reaction of 2-methylquinoline and 1-benzotriazolyl-2-propynones.

Reaction of 2-aminothiazole **2.22** with 1-benzotriazol-1-yl-3-phenylpropynone **2.14a** in a sealed tube at 120 °C in acetonitrile afforded the expected 5-phenylthiazolo [3,2-*a*]pyrimidin-7-one **2.23** in 54% yield (Scheme 2-7).



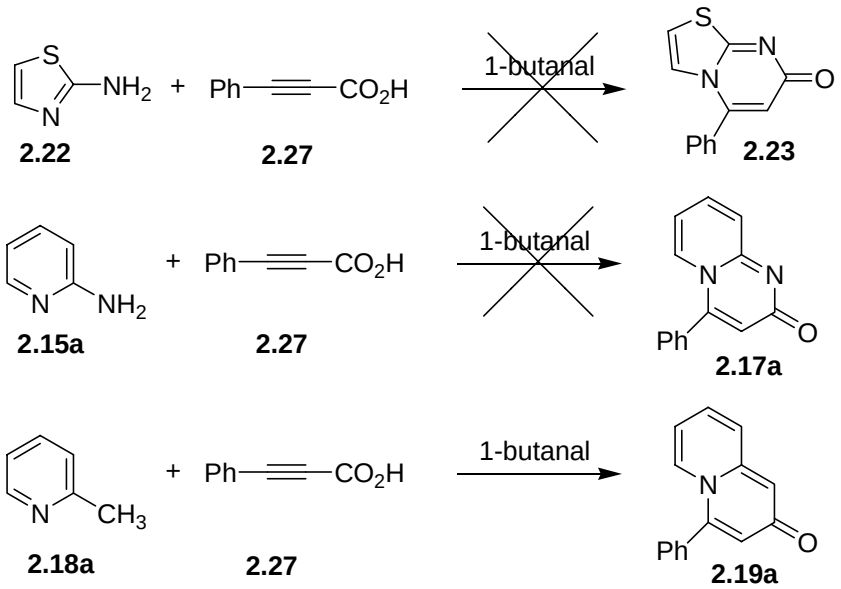
Scheme 2-7**.** Reaction of 2-aminothiazole and *N*-(phenylpropioyl)benzotriazole.

Synthesis of analogous pyrimido[2,1-*b*]benzothiazoles **2.26** from acetylenic acids **2.25** and 2-aminobenzothiazoles **2.24** has been previously reported (Scheme 2-8).[59]



Scheme 2-8. Syntheis of pyrimido[2,1-*b*]benzothiazoles.

Application of this procedure to the synthesis of pyrido[1,2-*a*]pyrimidin-2-one **2.17a**, 2*H*-quinolizin-2-one **2.19a** and thiazolo[3,2-*a*]pyrimidin-7-one **2.23** did not provide the desired products in the cases of pyrido[1,2-*a*]pyrimidin-2-one **2.17a** and thiazolo[3,2-*a*]pyrimidin-7-ones **2.23**. For 2*H*-quinolizin-2-one **2.19a**, only trace amounts of product were isolated from a complex reaction mixture after 2 days (Scheme 2-9).



Scheme 2-9. Attempted synthesis of **2.23, 2.17a and 2.19a** from 3-phenylpropiolic acid.

The following reaction mechanism is proposed for either pyrido[1,2-*a*]pyrimidin-2-ones **2.17** or 2*H*-quinolizin-2-one **2.19** although the other fused ring systems would be analogous. First conjugate addition of the pyridine nitrogen to the 1-benzotriazolyl-2-propynone forming in allenoic intermediate, followed by cyclocondensation, gave the corresponding fused heterocyclic ring (Figure 2-2).

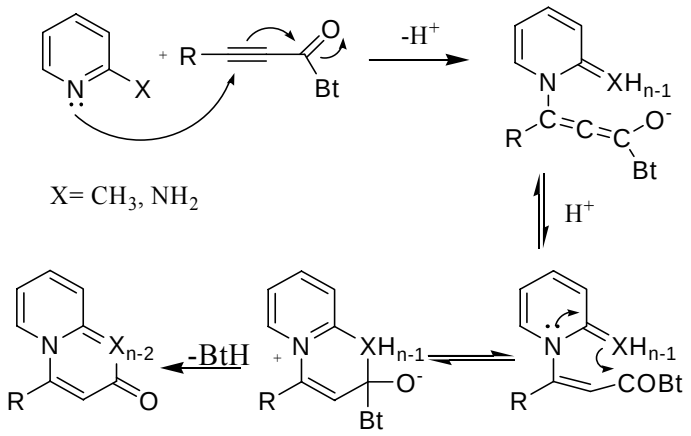


Figure 2-2. Mechanism of cyclization reaction.

2.3 Conclusion

In comparison, our *N*-acylbenzotriazole methodology offers shorter reaction times, cleaner conversion to products, and higher yields then the literature procedures to

synthesize pyrido[1,2-*a*]pyrimidin-2-ones. 1-Benzotriazolyl-2-propynones were also shown to be useful synthons for the synthesis of new heterocyclic systems.

2.4 Experimental

Melting points were determined using a Bristoline hot-stage microscope and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a 300 MHz NMR spectrometer in chloroform-*d* solution. Elemental and mass spectroscopy analyses were performed by Analytical Laboratories, Dept. of Chem., University of Florida. THF was distilled from sodium-benzophenone ketyl prior to use. All the reactions were performed in flame dried glassware and column chromatography was performed on silica gel (200–425 mesh).

2.4.1 General Procedure for the Preparation of Substituted 1-Benzotriazolyl-2-propynones 2.14a,b

To a solution of benzotriazole (2.96 g, 24.8 mmol) and thionyl chloride (5.55 mL, 20.8 mmol) in methylene chloride (20 mL), the appropriate acid (8.3 mmol) was added. The reaction mixture was stirred at room temperature for 3h. Solvent was removed under vacuum and the resultant solid was re-dissolved in ethyl acetate. The organic layer was washed with water, 1N NaOH (200 mL x 2), and brine. Recrystallization from ethyl acetate afforded the desired 1-benzotriazolyl-2-propynones in 80–95% yields.

1-Benzotriazol-1-yl-3-phenylpropynone (2.14a). White microcrystals (87%), mp 119–123 ^{o}C. ^{1}H NMR δ 7.31 – 7.63 (m, 4H), 7.73 – 7.78 (m, 1H), 7.84 – 7.87 (m, 2H), 8.22 (d, J = 8.1 Hz), 1H), 8.37 (d, J = 8.1 Hz, 1H). ^{13}C NMR δ 81.5, 94.8, 114.1, 118.2, 120.5, 127.2, 129.5, 130.6, 131.3, 132.4, 133.4, 145.9, 149.8. Anal. Calcd for $C_{15}H_9N_3O$: C, 72.86; H, 3.67; N, 16.99. Found: C, 72.55; H, 3.56; N, 16.98.

1-Benzotriazol-1-yl-oct-2-yn-1-one (2.14b). Yellow oil (95%). ^{1}H NMR δ 0.93 - 0.98 (m, 3H), 1.36 - 1.54 (m, 4H), 1.73 - 1.78 (m, 2H), 2.61(t, *J* = 7.2 Hz, 2H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 8.27 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR δ 13.9, 19.4, 22.1, 27.1,31.0, 100.4, 114.2, 120.3, 126.3, 126.5, 130.5, 130.9, 146.2, 150.2.

2.4.2 General Procedure for the Preparation of Pyrido[1,2-*a*]pyrimidin-2-ones 2.17a–c.

1-Benzotriazol-1-yl-3-phenylpropynone (200 mg, 0.90 mmol) and substituted 2-aminopyridine (0.90 mmol) were added to acetonitrile (3 mL) in a sealed tube and heated to 120 ^{o}C with stirring for 12 hours. Solvent was removed under vacuum and the crude mixture was separated by silica column chromatography (30% ethyl acetate/hexanes to remove benzotriazole, then 5% methanol/chloroform to elute product). Recrystallization from ethyl acetate afforded the desired pyrido[1,2-*a*]pyrimidin-2-ones in 71–88% yields.

4-Phenyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (2.17a). Yellow microcrystals (71%), mp 226–228 ^{o}C (Lit. mp 227–228 ^{o}C).[6] ^{1}H NMR δ 6.51 (s, 1H), 6.69 – 6.74 (m, 1H), 7.32 – 7.39 (m, 1H), 7.45 – 7.47 (m, 2H), 7.52 – 7.55 (m, 1H), 7.58 – 7.61 (m, 3H), 7.72 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR δ 112.6, 117.1, 125.3, 128.8, 129.6, 129.7, 130.8, 135.7, 148.6, 152.5, 168.1. Anal. Calcd For $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 74.90; H, 4.39; N, 12.54.

8-Methyl-4-phenylpyrido[1,2-*a*]pyrimidin-2-one (2.17b). Orange microcrystals (73%), mp 210–211 ^{o}C. ^{1}H NMR δ 2.15 (s, 3H), 6.45 (s, 1H), 7.27 – 7.32 (m, 1H), 7.38 – 7.45 (m, 4H), 7.56 – 7.60 (m, 3H).^{13}C NMR δ 18.0, 117.1, 122.7, 124.9, 126.9, 128.9, 129.7, 130.8, 131.1, 138.9, 148.5, 151.6, 168.3. Anal. Calcd For $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 75.20; H, 5.01; N, 12.08.

7-Methyl-4-phenylpyrido[1,2-*a*]pyrimidin-2-one (2.17c). Red microcrystals (71%), mp 160–162 ^{o}C. ^{1}H NMR δ 2.36 (s, 3H), 6.43 (s, 1H), 6.53 (d, 1H, *J* = 7.4 Hz), 7.13 (s, 1H), 7.40 – 7.43 (m, 2H), 7.56 – 7.61 (m, 4H). ^{13}C NMR δ 21.3, 115.5, 116.8, 123.1, 128.9, 129.0, 129.6, 130.8, 131.0, 147.9, 148.4, 152.6, 168.4. Anal. Calcd For $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 75.77; H, 5.36; N, 11.40.

2.4.3 General Procedure for the Preparation of Quinolizin-2-ones 2.19a–f.

1-Benzotriazol-1-yl-3-phenylpropynone or 1-benzotriazol-1-yl-oct-2-yn-1-one (0.90 mmol) and the appropriate 2-picoline derivative (0.90 mmol) were added to acetonitrile (3 mL) in a sealed tube and heated to 120 ^{o}C with stirring for 12 hours. Solvent was removed under vacuum and the crude mixture was separated by silica column chromatography (30% ethyl acetate/hexanes to remove benzotriazole, then 5% methanol/chloroform to elute product). Recrystallization from ethyl acetate afforded the substituted quinolizin-2-ones in 50–81 % yields.

4-Phenylquinolizin-2-one (2.19a). Amber microcrystals (61%), mp 189-191 ^{o}C. ^{1}H NMR δ 6.49 – 6.54 (m, 1H), 6.74 (d, *J* = 2.7 Hz, 1H), 6.85 (d, *J* = 2.7 Hz, 1H), 7.11 – 7.16 (m, 1H), 7.26 – 7.34 (m, 1H), 7.37 – 7.54 (m, 3H), 7.59 – 7.61 (m, 2H), 7.71 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR δ 111.5, 112.4, 124.4, 124.8, 128.4, 128.7, 129.1, 129.4, 129.6, 130.3, 132.9, 145.0, 146.0, 175.4. HRMS (EI) Found $[M]^+$ 221.0852; $C_{15}H_{11}NO$ requires 221.0841.

2-Oxo-4-phenyl-2*H*-quinolizin-1-carbonitrile (2.19b). Amber microcrystals (81%), mp 170-172 ^{o}C. ^{1}H NMR δ 6.76 – 6.82 (m, 2H), 7.30 (s, 1H), 7.46 – 7.49 (m, 2H), 7.55 – 7.58 (m, 1H), 7.62 – 7.65 (m, 3H), 7.82 – 7.91 (m, 2H). ^{13}C NMR δ 94.9, 113.8, 115.5, 122.5, 125.2, 129.0, 129.2, 129.9, 130.9, 131.3, 131.7, 133.5, 147.05, 148.4.

Anal. Calcd For $C_{16}H_{10}N_2O$: C, 78.03; H, 4.09; N, 11.38. Found: C, 71.82; H, 3.96; N, 11.97.

1,4-Diphenylquinolizin-2-one (2.19c). Amber microcrystals (50%), mp 223–225 ^{o}C. ^{1}H NMR δ 6.43 (ddd, *J* = 7.2, 6.3, 1.2 Hz, 1H), 6.93 (s, 1H), 6.95 (ddd, *J* = 7.5, 6.3, 1.2 Hz, 1H), 7.22 (d, *J* = 9.3 Hz, 1H), 7.40 – 7.44 (m, 3H), 7.50 – 7.56 (m, 4H), 7.60 – 7.63 (m, 3H), 7.73 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR δ 111.4, 123.3, 123.8, 124.4, 127.6, 127.9, 128.8, 129.2, 129.5, 129.7, 130.1, 131.0, 133.5, 134.8, 142.6, 145.1, 173.7. Anal. Calcd For $C_{21}H_{15}NO$: C, 84.82; H, 5.08; N, 4.71. Found: C, 84.29; H, 5.01; N, 4.66.

1-Methyl-4-phenylquinolizin-2-one (2.19d). Dark purple oil (51%). ^{1}H NMR δ 2.36 (s, 3H), 6.41 (t, *J* = 6.3 Hz, 1H), 6.80 (s, 1H), 7.07 – 7.12 (m, 1H), 7.39 – 7.42 (m, 2H), 7.44 (d, *J* = 4.8 Hz, 1H), 7.48 – 7.55 (m, 3H), 7.68 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR δ 10.3, 111.0, 118.1, 122.0, 122.4, 127.7, 129.1, 129.4, 129.9, 130.0, 133.5, 141.6, 144.3, 174.4. Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 66.53; H, 4.85; N, 5.48.

4-Pentylquinolizin-2-one (2.19e). Dark purple oil (39%). ^{1}H NMR δ 0.95 (m, 3H), 1.37 –1.46 (m, 4H), 1.73 (t, *J* = 7.5 Hz, 2H), 2.83 (t, *J* =7.9 Hz, 2H), 6.54 (d, *J* = 4.2 Hz, 1H), 6.63–6.68 (m, 1H), 6.75 (d, *J* = 2.7 Hz, 1H), 7.06 – 7.11 (m, 1H), 7.16 – 7.19 (m, 1H), 7.82 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR δ 13.9, 22.3, 26.2, 31.3, 32.4, 111.2, 112.6, 122.7, 125.3, 127.2, 128.0, 145.0, 145.2, 175.8. HRMS (EI) Found $[M]^+$ 215.1300; $C_{14}H_{17}NO$ requires 215.1310.

9-Methyl-4-phenylquinolizin-2-one (2.19f). Red microcrystals (53%), mp 206-208 ^{o}C. ^{1}H NMR δ 2.40 (s, 3H), 6.42 (t, *J* = 7.2 Hz, 3H), 6.79 (s, 2H), 7.00 (d, *J* = 6.6 Hz, 1H), 7.42 – 7.45 (m, 2H), 7.57 –7.62 (m, 4H). ^{13}C NMR δ 19.6, 109.0, 111.4, 124.1,

127.9, 128.0, 129.1, 129.5, 130.1, 131.0, 133.6, 145.3, 146.5, 175.8. Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.80; N, 5.95. Found: C, 68.25; H, 5.57; N, 5.56.

2.4.4 General Procedure for the Preparation of Pyrido[1,2-a]quinolin-3-ones 2.21a,b and 5-Phenylthiazolo[3,2-a]pyrimidin-7-one (2.23).

1-Benzotriazol-1-yl-3-phenylpropynone or 1-benzotriazol-1-yl-oct-2-yn-1-one (0.90 mmol) and the appropriate substituted 2-methylquinoline or 2-aminothiazole (0.90 mmol) were added to acetonitrile (3 mL) in a sealed tube and heated to 120 ^{o}C with stirring for 12 hours. Solvent was removed under vacuum and the crude mixture was separated by silica column chromatography (30% ethyl acetate/hexanes to remove benzotriazole, then 5% methanol/chloroform to elute product). Recrystallization from ethyl acetate afforded the pyrido[1,2-*a*]quinolin-3-ones in 40 % yield and 5-phenylthiazolo[3,2-*a*]pyrimidin-7-one in 54% yield.

1-Phenylpyrido[1,2-*a*]quinolin-3-one (2.21a). Dark purple oil (40%). ^{1}H NMR δ 6.57 (d, J = 3 Hz, 1H), 6.79 (d, J = 3 Hz, 1H), 6.95 – 7.08 (m, 3H) 7.22 – 7.27 (m, 1H), 7.31 – 7.36 (m, 3H), 7.38 – 7.45 (m, 3H), 7.52 – 7.55 (m, 1H). ^{13}C NMR δ 114.3, 123.1, 124.0, 125.4, 125.6, 125.8, 127.4, 127.6, 128.2, 129.3, 129.4, 130.0, 135.3, 137.3, 145.7, 148.6, 177.7. Anal. Calcd For $C_{19}H_{13}NO$: C, 84.11; H, 4.83; N, 5.16. Found: C, 84.82; H, 4.72; N, 5.11.

1-Pentylpyrido[1,2-*a*]quinolin-3-one (2.21b). Dark purple oil (40%). ^{1}H NMR δ 0.81 (t, J = 6.9 Hz, 3H), 1.17 – 1.22 (m, 4H), 1.61 (t, J = 7.2 Hz, 2H), 3.05 (t, J = 7.8 Hz, 2H), 6.47 (d, J = 2.4 Hz, 1H), 6.77 (d, J = 2.4 Hz, 1H), 6.95 (d, J = 9.0 Hz, 1H), 7.24 – 7.28 (m, 2H), 7.49 – 7.59 (m, 2H). ^{13}C NMR δ 13.8, 22.2, 29.9, 31.1, 34.9, 113.5, 121.4, 123.5, 124.4, 125.9, 126.0, 127.9, 128.3, 219.2, 134.8, 145.3, 151.2, 177.7. Anal. Calcd For $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 80.47; H, 7.33; N, 5.25.

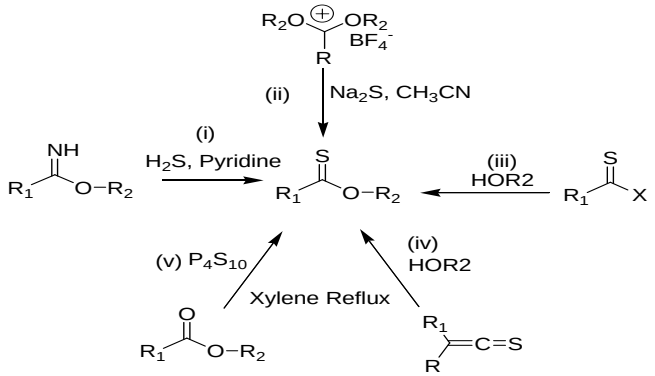
5-Phenylthiazolo[3,2-*a*]pyrimidin-7-one (2.23). White plates (54%), mp 161-164 ^{o}C (Lit. mp 191–194 ^{o}C).[15] ^{1}H NMR δ 6.15 (s, 1H), 7.22 (d, *J* = 4.2 Hz, 1H), 7.35 (d, *J* = 4.8 Hz, 1H), 7.59 – 7.65 (m, 5H). ^{13}C NMR δ 98.2, 109.8, 110.8, 123.3, 128.6, 129.2, 130.7, 131.2, 147.9, 166.5. Anal. Calcd For $C_{12}H_8N_2OS$: C, 63.14; H, 3.53; N, 12.27. Found : C, 60.14; H, 3.48; N, 12.07. *Note while the mp was considerably lower then what the literature reported the author feels that since the product was isolated as an amorphous solid the mp would be lower than uniform crystals.

CHAPTER 3
DEVELOPMENT OF BENZOTRIAZOLE ASSISTED THIOACYLATION METHODOLOGIES

3.1 Introduction

Thionoesters (R-C(S)-OR) have been a focus of interest due to their different reactivities relative to their oxygen analogues.[60,61] For example they can be desulfanated using Raney nickel to form ethers. [62] This is a good path to convert esters to ethers while avoiding problems associated with steric and functional limitations.[63] Thionoesters have been shown to react with DAST under mild conditions to form α,α-difluoroethers, which are compounds of current interest.[64] 1,3,4-Oxadiazoles[65] can also be synthesized using thionoesters as starting material, these compounds have generated considerable interests due to their use as plant cell growth hormones, herbicides, and fungicides.[66,67] Thionoesters have recently been found to be effective chain transfer agents in various polymerizations including styrene, methyl acrylate and other related olefins.[68]

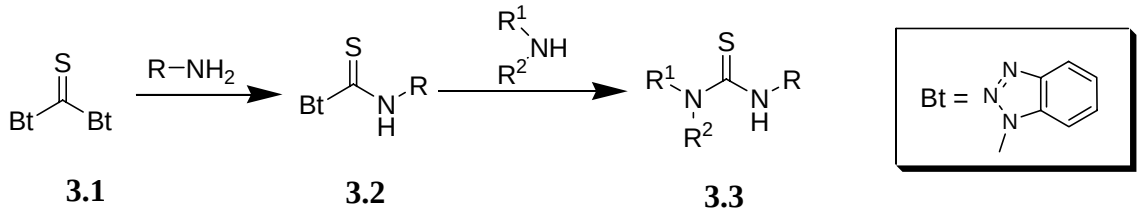
Several examples of various methodologies for the synthesis of thionoesters are depicted on Scheme 3-1 below.



Scheme 3-1. Classical methods for the synthesis of thionoesters.

Example (i) is sulfur-hydrolysis of iminoesters with hydrogen sulfide in pyridine. Unfortunately thioamides are often a major side product and the methodology was limited in scope[69,70]. Example (ii)is sulfo-hydrolysis of dialkoxycarbonium ions, which often results in mixtures requiring lengthy purification techniques.[71,72] Examples (iii) and (iv) are alcoholysis of thioacyl halides[73] and thioketenes[74] to thionoesters. Thioacyl halides are generally very unstable, only thiobenzoyl chlorides see much use. Aliphatic thioacyl halides decompose even at -70 ^{o}C.[75] Thioketenes have a similar problem to thioacyl halides in that they are also very unstable and dimerize rapidly unless kept at a very low temperature. Direct thionation of an ester with phosphorus sulfide reagents to give the corresponding thionoester is shown in example (v) on Scheme 2.1.[76] This is probably the best procedure for synthesizing thionoesters but the reaction conditions are long and harsh (refluxing xylene or toluene), and is limited to compounds which do not have sensitive functional groups.

The Katritzky group has applied *N*-acylbenzotriazoles to the syntheses of amides,[77] β-keto sulfones,[78] α-substituted β-ketonitriles,[79] oxazolines and thiazolines,[80] and *C*-acylated-pyrroles and -indoles.[81] The Katritzky group recently reported the application of thioacylating reagent, bis(benzotriazolyl)methanethione **3**.**1**, in the preparation of unsymmetrical di- and tri-substituted thioureas **3.3** by intermediate 1-(alkyl/arylthiocarbamoyl) benzotriazoles **3.2**[33] (Scheme 3-2).

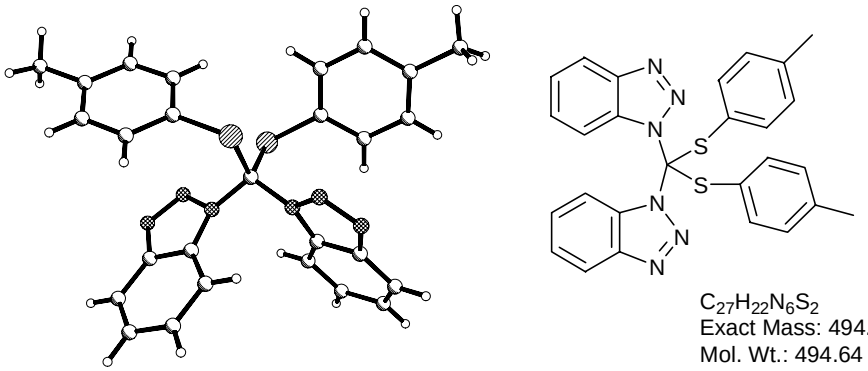


Scheme 3-2. Preparation of unsymmetrical di- and tri-substituted thioureas **3.3**

This work has been greatly extended by preparing a range of reagents for thioacylation (RCSBt), thiocarbamoylation (RR'NCSBt), aryl/alkoxythioacylation (ROCSBt), and aryl/alkylthiothioacylation (RSCSBt). This report will detail the work completed on reagents for thioacylation, namely thioacyl nitrobenzotriazoles. Reactions of thioacyl nitrobenzotriazoles with oxygen nucleophiles gave the corresponding thionoesters in good yield.

3.2 Results and Discussion

It should be noted that Rachel M. Witek of the Katritzky group found that the direct reaction of bis(benzotriazolyl)methanethione 3.1 with Grignard reagents provides low yields (12–34%) of bis(benzotriazolyl)diarylsulfidemethanes (Figure 3-1) instead of thiocarbonylbenzotriazoles. Due to these unsatisfactory results alternate routes to thiocarbonylbenzotriazoles were investigated.



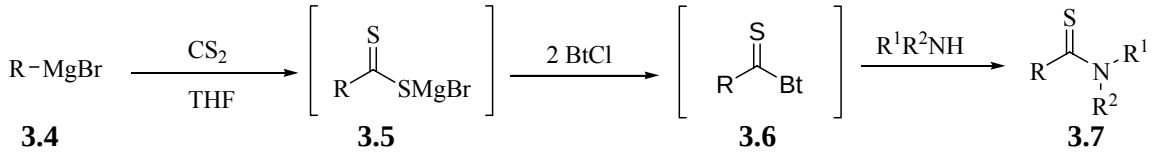
$C_{27}H_{22}N_6S_2$
Exact Mass: 494.13
Mol. Wt.: 494.64
C, 65.56; H, 4.48; N, 16.99; S, 12.97

Figure 3-1. X-ray structure of bis(benzotriazolyl)-di-(4-methylphenylylthio)methane.

In previously reported syntheses of thioamides in one-pot reactions from Grignard reagents, carbon disulfide, and amines mediated by 1-trifluoromethyl-sulfonylbenzotriazole;[82a,b] the putative intermediate thiocarbonyl benzotriazoles **3.6** were evidently formed, but were not isolated. Decomposition of analogous methyl-substituted thioacylimidazoles has been reported.[83] 1-Chlorobenzotriazole is used (instead of 1-

trifluoromethylsulfonyl-benzotriazole) as the mediating reagent which allows isolation of **3.6** in some cases (Scheme 3-3).

Rachel M. Witek prepared thiocarbonylbenzotriazoles **3.6a-d** from carbon disulfide, 1-chlorobenzotriazole and the respective Grignard or organolithium reagents (Table 3.1). The benzenoid thiocarbonylbenzotriazoles (63–89%) are all stable reddish solids. Benzotriazol-1-yl-4-methylphenyl methanethione **3.6a** displays the characteristic ^{1}H NMR shifts for benzotriazole overlapping with aromatic shifts of the p-tolyl group δ7.39 (d, J = 8.4 Hz, 2H), 7.55 (t, J = 7.5 Hz, 1H), 7.71 (t, J = 7.5 Hz, 1H), 8.14–8.19 (m, 3H), 8.39 (d, J = 8.4 Hz, 1H)}. A ^{13}C NMR shift ~170 ppm is common for the thiocarbonyl in compounds **3.6a–d**.



Scheme 3-3. Preparation of thiocarbonylbenzotriazoles **3.6a-d.**

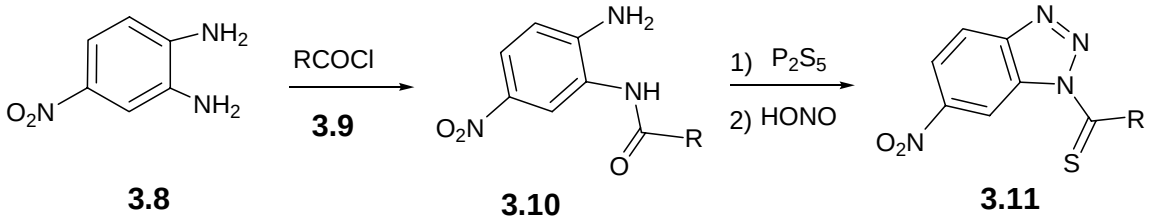
Table 3-1. Preparation of thiocarbonylbenzotriazoles **3.6a–d.**

3.6	R	% Yield
a	4-Tolyl	63
b	4-Methoxyphenyl	89
c	Phenyl	76
d	4-Chlorophenyl	42

One limitation of this method is that it is restricted to Grignard compatible functionalities. In addition, while benzenoid aryl Grignard reagents react quite smoothly to give thiocarbonylbenzotriazoles **3.6**, only poor yields are attained for alkyl, alkynyl, and heteroaryl Grignard reagents. In Rachel's hands, attempts to obtain *n*-butyl substituted thiocarbonylbenzotriazole in higher yield by conducting the reactions at 0 ^{o}C and at -78 ^{o}C failed. Likewise conversion of *n*-butyllithium to *n*-butylzinc bromide or n-

butylcuprous bromide for reactions with carbon disulfide and 1-chlorobenzotriazole also failed.

The stability of non-benzenoid thiocarbonylbenzotriazoles thus appears to be poor. Rapoport utilized the route of Scheme 3-4 to obtain aliphatic thiocarbonyl-1*H*-6-nitrobenzotriazoles in good yields (48-67%).[36a,b] Apparently, the electron-withdrawing nitro group on the benzotriazole moiety improves the stability and allows the isolation of aliphatic thiocarbonylbenzotriazoles **3.11**. Following this methodology, several novel aliphatic and aromatic thiocarbonyl-1*H*-6-nitrobenzotriazoles **3.11b–g** were prepared (compound **3.11a** was previously synthesized by Rapoport) **(**Scheme 3-4, Table 3-2).



Scheme 3-4. Preparation of thiocarbonyl-1*H*-6-nitrobenzotriazoles.

Table 3-2. Aliphatic and aromatic thiocarbonyl-1*H*-6-nitrobenzotriazoles **3.11a–g.**

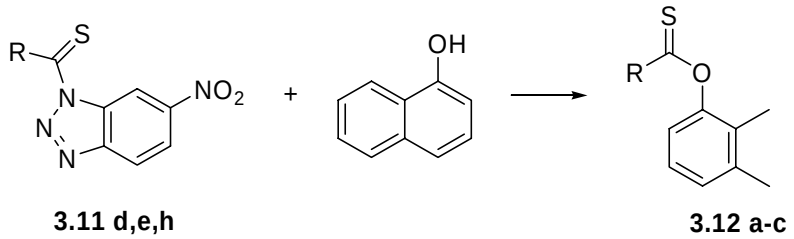
3.11	Acid Chloride 3.9 R =	Amide 3.10 (% yield)	Thiocarbonyl-6-nitrobenzotriazole 3.11 (% yield from 3.10)
a	Ethyl	84	52
b	4-Methylphenyl	98	80
c	2-Furanyl	95	80
d	4-Nitrophenyl	83	69
e	4-Methoxyphenyl	86	66
f	4-Bromophenyl	99	45
g	Pentyl	81	53
h	2-Thienyl	91	81

Treatment of 4-nitrobenzene-1,2-diamine **3.8** with the respective acid chlorides **3.9** gave regioselectively the intermediate amides **3.10** (83–99%). Resonance and the inductive effect of the nitro group lowers the nucleophilicity of the amino group in the para position, leaving the meta amino group to attack the carbonyl of the acid chloride

3.9. Amides **3.10** were converted to thioamides in crude yields of 59–96% by stirring at room temperature with phosphorus pentasulfide (Scheme 2-3, Table 2-2). Thioamides were cyclized by treatment with sodium nitrite and acetic acid to afford thiocarbonyl-1*H*-6-nitrobenzotriazoles **3.11a–g** in 45–80% yields from the corresponding amides **3.10**.

Thiocarbonyl-6-nitro-1*H*-benzotriazoles **3.11a–g** are all stable reddish solids. (6-Nitrobenzotriazole-1-yl)propane-1-thione **3.11a** shows the characteristic ^{1}H NMR {8.31 (d, J = 8.9 Hz, 1H), 8.44 (dd, J = 8.9, 1.8 Hz, 1H), 9.74 (s, 1H)} and ^{13}C NMR shifts113.1, 121.2, 121.7, 131.7, 149.0, 149.4), which correspond to 6-nitro-1H-benzotriazole. The thiocarbonyl ^{13}C NMR shift of thiocarbonyl-6-nitro-1*H*-benzotriazoles **3.11** is further downfield compared to thiocarbonylbenzotriazoles **3.6** and is found at 211.6 ppm for **3.11a**. Although this method is general and alkyl derivatives are obtained in moderate overall yields (44–72%), from 4-nitrobenzene-1,2-diamine **3.8** and the respective acid chlorides **3.9**, the lengthy 3-step procedure is a drawback. Thus, the Grignard method of Scheme 2 is the preferred means of obtaining arylthiocarbonyl-benzotriazoles while Rapoport's synthesis is preferred for alkyl, alkynyl, and heteroaryl thiocarbonylbenzotriazoles.

Thiocarbonyl-6-nitrobenzotriazoles **3.11 e,d,h** were reacted with 1-naphthol providing thionoesters **3.12a-c** in 62–99% yields (Scheme 3-5, Table 3-3).



Scheme 3-5. Preparation of thionoesters.

Table 3-3 Thionoesters **3.12a-c**

Thionoesters 3.12	Alcohol	Thioacylating Agent R =	Yield (%)
a	1-Naphthyl	4-Methoxyphenyl (3.10e)	88
b	1-Naphthyl	4-Nitrophenyl (3.10d)	99
c	1-Naphthyl	2-Thienyl (3.10h)	62

3.3 Conclusion

Application of benzotriazole reagents for aryl/alkoxythioacylation (ROCSBt) to the syntheses of several novel thionoesters has been successfully developed. Advantages of benzotriazole methods are primarily that use of unstable or hazardous reagents is avoided, the mild conditions employed are tolerable of a large variety of functional groups, and yields are comparable and in many cases higher than previously reported methods.

3.4 Experimental Section

Melting points were determined using a Bristoline hot-stage microscope and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a 300 MHz NMR spectrometer in chloroform-*d* solution. Elemental and mass spectroscopy analyses were performed by Analytical Laboratories, Dept. of Chem., University of Florida. THF was distilled from sodium-benzophenone ketyl prior to use. All the reactions were performed under a nitrogen atmosphere and in flame dried glasswares. Column chromatography was performed on silica gel (200–425 mesh).

3.4.1 General Pprocedure for the Preparation of 2-Amino-5-nitrophenylamides 3.10a–h.

Et_3N (3.0 g, 30 mmol) was added to a solution of 4-nitrobenzene-1,2-diamine (3.06 g, 20 mmol) in THF (100 mL) at –40 ^{o}C, followed by dropwise addition of the respective acid chloride (20 mmol). The mixture was stirred at –40 ^{o}C for 3h and at rt overnight. The precipitate was filtered off and the filtrate evaporated to dryness *in vacuo*.

The residue was recrystallized from EtOH to afford the desired 2-amino-5-nitrophenylamides **3.10a–h** in 81–99 % yields.

***N*-(2-Amino-5-nitrophenyl)propionamide (3.10a).** Yellow microcrystals (84 %), mp 189–191 ^{o}C, (Lit.[23] mp 191 ^{o}C). ^{1}H NMR δ 1.10 (t, *J* = 7.6 Hz, 3H), 2.38 (q, *J* = 7.6 Hz, 2H), 6.49 (s, 2H), 6.76 (d, *J* = 9.0 Hz, 1H), 7.84 (dd, *J* = 9.0, 2.5 Hz, 1H), 8.27 (d, *J* = 2.5 Hz, 1H), 9.13 (s, 1H). ^{13}C NMR δ 9.6, 28.9, 113.6, 121.2, 121.7, 122.6, 135.5, 148.9, 172.6.

***N*-(2-Amino-5-nitrophenyl)-4-methylbenzamide (3.10b).** Yellow needles (98%), mp 197–198°C. ^{1}H NMR δ 2.39 (s, 3H). 6.59 (s, 2H), 6.82 (d, *J* = 9.1 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.91 (d, *J* = 9.2 Hz, 1H), 7.93 (d, *J* = 8.1 Hz, 2H), 8.15 (d, *J* = 2.6 Hz, 1H), 9.68 (s, 1H). ^{13}C NMR δ 21.0, 113.9, 121.4, 123.5, 128.0, 128.8, 131.4, 135.4, 141.6, 150.6, 165.9. Anal. Calcd. For $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 62.35; H, 4.76; N, 15.13.

***N*-(2-Amino-5-nitrophenyl)furan-2-carboxamide (3.10c).** Yellow needles (95 %), mp 176–178°C. ^{1}H NMR δ 6.61 (s, 2H), 6.71 (dd, *J* = 3.3, 1.5 Hz, 1H), 6.81 (d, *J* = 9.0 Hz, 1H), 7.33 (d, *J* = 3.6 Hz, 1H), 7.91–7.94 (m, 2H), 8.06 (d, *J* = 2.4 Hz, 1H), 9.69 (s, 1H). ^{13}C NMR δ 112.1, 113.9, 114.9, 120.4, 123.8, 135.4, 145.6, 147.4, 150.9, 157.0, 168.0. Anal. Calcd. For $C_{11}H_9N_3O_4$: C, 53.44; H, 3.67; N, 17.00. Found: C, 54.65; H, 3.28; N, 13.25.

***N*-(2-Amino-5-nitrophenyl)-4-nitrobenzylamide (3.10d).** Brown needles (83%), mp 303–305 ^{o}C. ^{1}H NMR δ 6.58 (s, 2H), 6.84 (d, *J* = 9 Hz, 1H), 7.93 (dd, *J* = 9, 2.4 Hz, 1H), 8.25–8.30 (m, 4H), 8.38 (s, 1H). ^{13}C NMR δ113.6, 122.8, 123.1, 123.8, 129.3,

129.6, 129.7, 148.0, 148.4, 150.8, 193.5. Anal. Calcd. For $C_{13}H_{10}N_4O_5$: C, 51.66; H, 3.33. Found: C, 52.03; H, 3.39.

***N*-(2-Amino-5-nitrophenyl)-4-methoxybenzylamide (3.10e).** Brown needles (86%), mp 221–224 ^{o}C. ^{1}H NMR δ 3.84 (s, 3H), 6.59 (s, 2H), 6.80 (d, *J* = 9.3 Hz, 1H), 7.08 (d, *J* = 9.3 Hz, 2H), 7.91 (dd, *J* = 9.3, 2.7 Hz, 1H), 8.00 (d, *J* = 2.7 Hz, 1H), 8.11 (d, *J* = 2.4 Hz, 1H), 9.62 (s, 1H). ^{13}C NMR δ 55.6, 113.6, 114.0, 121.7, 123.7, 130.1, 130.8, 135.5, 150.9, 162.1, 165.6, 204.5. Anal. Calcd. For $C_{14}H_{13}N_3O_3$: C, 58.53; H, 4.56; N, 14.63. Found: C, 58.55; H, 4.57; N, 14.09.

***N*-(2-Amino-5-nitrophenyl)-4-bromobenzylamide (3.10f).** Brown needles (99%), mp 222–223 ^{o}C. ^{1}H NMR δ 6.65 (s, 2H), 6.80 (d, *J* = 9 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.91–7.98 (m, 3H), 8.11 (s, 1H), 9.83 (s, 1H). ^{13}C NMR δ 114.0, 121.1, 124.0, 125.6, 130.3, 131.4, 133.5, 135.4, 151.0, 161.8, 165.4. Anal. Calcd. For $C_{13}H_{10}NBrO_2$: C, 46.45; H, 3.00; N, 12.50. Found: C, 46.34; H, 2.93; N, 11.89.

***N*-(2-Amino-5-nitrophenyl)hexylamide (3.10g).** Brown needles (81%), mp 130–131 ^{o}C. ^{1}H NMR δ 0.90 (t, *J* = 6.6 Hz, 3H), 1.32–1.34 (m, 4H), 1.62 (quintet, *J* = 6.6 Hz, 2H), 2.37 (t, *J* = 6.6 Hz, 2H), 6.49 (s, 2H), 6.78 (d, *J* = 9 Hz, 1H), 7.85 (dd, *J* = 9.0, 2.4 Hz, 1H), 8.31 (d, *J* = 2.4 Hz, 1H), 9.16 (s, 1H). ^{13}C NMR δ 14.0, 22.1, 24.9, 31.1, 36.0, 113.8, 121.2, 121.9, 122.7, 135.7, 148.8, 172.1. Anal. Calcd. For $C_{12}H_{17}N_3O_3$: C, 57.36; H, 6.82; N, 16.72. Found: C, 57.88; H, 7.04; N, 15.97.

***N*-(2-Amino-5-nitrophenyl)thiophene-2-carboxamide (3.10h).** Brown needles (91%), mp 192–196 ^{o}C. ^{1}H NMR δ 6.65 (s, 2H), 6.81 (d, *J* = 9 Hz, 1H), 7.22–7.25 (m, 1H), 7.86–7.95 (m, 2H), 8.03–8.09 (m, 2H), 9.81 (s, 1H). ^{13}C NMR δ 114.0, 120.8,

124.0, 128.2, 129.9, 131.9, 135.5, 139.5, 151.1, 160.8, 167.6. Anal. Calcd. For $C_{11}H_9N_3O_3S$: C, 50.18; H, 3.45; N, 15.96. Found: C, 49.98; H, 3.29; N, 15.43.

3.4.2 General Procedure for the Synthesis of Aliphatic and Aromatic Thiocarbonyl-1*H*-6-nitrobenzotriazoles 3.11a–g.

Phosphorus pentasulfide (2.22g, 10 mmol) was mixed with Na_2CO_3 (0.54 g, 5 mmol) in dry THF (150 mL). The mixture was stirred at rt for 1h and then cooled to 0 ^oC. The amide **9** (10 mmol) was added in one portion and the resulting mixture stirred at 0 ^oC for 3 hrs and rt for 10 hrs. The mixture was filtered and the filtrate evaporated to dryness, the residue was dissolved in EtOAc (100 mL) and washed with 5 % $NaHCO_3$ (2 x 30 mL), and the aqueous layers back-extracted with EtOAc (100 mL). The combined organic layers were washed with brine, dried with $MgSO_4$ and evaporated to obtain a residue. The residue was placed on a silica-gel column and eluted with hexanes/ EtOAc (5:1) to give thioamides in crude yields of 59–96 %.

Sodium nitrite (0.21 g, 3 mmol) was added to a stirred solution of the obtained thioamide (2 mmol) dissolved by gentle warming in aqueous acetic acid 95 % (25 mL) and then cooled to 0 ^oC. The resulting mixture was stirred at 0 ^oC for 45 min., then ice-cold water (100 mL) was added and the precipitated product was filtered and washed with water. Compound **3.11g** was an exception requiring sonication and extraction with EtOAc, which entailed washing the aqueous solution three times with 50 mL EtOAc, collection of the organic layers and washing them with water (2 x 30mL) and brine (40 mL), drying with sodium sulfate, and filtration. The obtained solid was dried *in vacuo* overnight to afford the desired thiocarbonyl-1*H*-6-nitrobenzotriazoles **3.11a–h** in 45–81 % yields from the amides **3.10a-h**.

(6-Nitrobenzotriazol-1-yl)propane-1-thione (3.11a). Orange microcrystals (52 %), mp 107–109 ^{o}C, (Lit.[23] mp 108 ^{o}C). ^{1}H NMR δ 1.54 (t, *J* = 7.1 Hz, 3H), 3.79 (q, *J* = 7.1 Hz, 2H), 8.31 (d, *J* = 9.0 Hz, 1H), 8.44 (dd, *J* = 9.0, 1.8 Hz, 1H), 9.74 (s, 1H). ^{13}C NMR 13.4, 40.6, 113.1, 121.2, 121.7, 131.7, 149.0, 149.4, 211.6.

(4-Methylphenyl)-(6-nitrobenzotriazol-1-yl)methanethione (3.11b). Red microcrystals (80 %), mp 140–141 ^{o}C. ^{1}H NMR δ 2.45 (s, 3H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H), 8.32 (d, *J* = 9.0 Hz, 1H), 8.44 (dd, *J* = 9.0, 1.1 Hz, 1H), 9.42 (s, 1H). ^{13}C NMR δ21.8, 112.1, 121.2, 121.5, 129.1, 131.2, 133.1, 139.4, 145.1, 148.8, 148.9, 200.5. Anal. Calcd. For $C_{14}H_{10}N_4O_2S$: C, 56.37; H, 3.38; N, 18.78. Found: C, 56.65; H, 3.29; N, 18.69.

Furan-2-yl-(6-nitrobenzotriazol-1-yl)-methanethione (3.11c). Orange microcrystals (80%), mp 162 ^{o}C. ^{1}H NMR δ 6.79 (dd, *J* = 3 Hz, 1.5 Hz, 1H), 7.66 (d, *J* = 3.6 Hz, 1H), 8.00 (d, *J* = 0.9 Hz, 1H), 8.32 (d, *J* = 9 Hz, 1H), 8.43 (dd, *J* = 9 Hz , 2.1 Hz, 1 H), 9.47 (d, *J* = 1.8 Hz, 1H). ^{13}C NMR δ 112.1, 114.4, 121.2, 121.4, 122.4, 132.9, 148.6, 148.8, 151.8, 154.3, 180.1. Anal. Calcd. For $C_{11}H_6N_4O_3S$: C, 48.17; H, 2.21. Found C, 47.83; H, 2.12.

(4-Nitrophenyl)-(6-nitrobenzotriazol-1-yl)methanethione (3.11d). Orange needles (69%), mp 174 ^{o}C. ^{1}H NMR δ 7.46 (d, *J* = 8.7 Hz, 2H), 7.82 (d, *J* = 8.7 Hz, 2H), 7.93 (d, *J* = 8.7 Hz, 1H), 8.02 (d, *J* = 8.7 Hz, 2H), 9.00 (d, *J* = 1.8 Hz, 1H). ^{13}C NMR δ 114.3, 114.7, 121.1, 123.4, 123.9, 130.9, 131.4, 136.4, 150.2, 166.0, 208.0. Anal. Calcd. For $C_{13}H_7N_5O_4S$: C, 47.42; H, 2.14 ; N, 21.27. Found C, 47.50; H, 2.02 ; N, 20.93.

(4-Methoxyphenyl)-(6-nitrobenzotriazol-1-yl)methanethione (3.11e). Orange needles (66%), mp 162 ^{o}C. ^{1}H NMR δ 3.93 (s, 3H), 6.98 (d, *J* = 9.0 Hz, 2H), 7.86 (d, *J* =

9.0 Hz, 2H), 8.31 (d, *J* = 9.0 Hz, 1H), 8.42 (dd, *J* = 9.0 Hz, 2.1 Hz, 1H), 9.37 (d, *J* = 2.1 Hz, 1H). ^{13}C NMR δ 55.8, 112.0, 113.9, 112.1, 133.3, 134.0, 134.7, 148.6, 148.9, 164.8, 198.4. Anal. Calcd. For $C_{14}H_{10}N_4O_3S$: C, 53.50; H, 3.21; N, 17.82. Found C, 53.61; H, 3.14; N, 17.62.

(4-Bromophenyl)-(6-nitro-benzotriazol-1-yl)methanethione (3.11f). Orange micro-crystals (45 %), mp 170 ^{o}C. ^{1}H NMR δ 7.67–7.74 (m, 4H), 8.39 (d, *J* = 9 Hz, 1H), 8.52 (dd, *J* = 9, 1.8 Hz, 1H), 9.54 (d, *J* = 2.1 Hz, 1H). ^{13}C NMR δ 112.1, 121.4, 121.9, 128.8, 131.6, 132.1, 132.8, 140.6, 149.0, 149.1, 199.6. Anal. Calcd. For $C_{13}H_7BrN_4O_2S$: C, 42.99; H, 1.94. Found: C, 42.81; H, 1.79.

(6-Nitrobenzotriazol-1-yl)-1-hexylthioamide (3.11g). Yellow microcrystals (53%), mp 94–97 ^{o}C. ^{1}H NMR δ 0.94 (t, *J* = 6.9 Hz, 3H), 1.37–1.52 (m, 4H), 1.95–2.05 (m, 2H), 3.78 (t, *J* = 7.5 Hz, 2H), 8.30 (d, *J* = 9.0 Hz, 1H), 8.44 (dd, *J* = 9.0, 1.8 Hz, 1H), 9.79 (d, *J* = 2.1 Hz, 1H). ^{13}C NMR δ 13.9, 22.3, 29.4, 31.1, 47.6, 113.1, 121.2, 121.8, 131.7, 149.1, 149.4, 210.7. Anal. Calcd. For $C_{12}H_{14}N_4O_2S$: C, 51.78; H, 5.07; N, 20.13. Found: C, 52.14; H, 5.12; N, 19.79.

(6-Nitrobenzotriazol-1-yl)thiophen-2-yl methanethione (3.11h). Orange microcrystals (81%), mp 134 ^{o}C. ^{1}H NMR δ 7.25 (dd, *J* = 4.0, 1.2 Hz, 1H), 7.97 (d, *J* = 4.8 Hz, 1H), 8.10 (d, *J* = 4.0 Hz, 1H), 8.31 (d, *J* = 8.7 Hz, 1H), 8.42 (d, *J* = 8.7 Hz, 1H), 9.45 (s, 1H). ^{13}C NMR δ 112.3, 121.2, 121.4, 129.2, 133.0, 136.5, 140.5, 146.6, 148.7, 187.3. Anal. Calcd. For $C_{11}H_6N_4O_2S_2$: C, 45.51; H, 2.08, N, 19.30. Found: C, 44.66; H, 1.90; N, 18.45.

3.4.3 General Procedure for the Preparation of Thionoesters 3.12a–c.

The appropriate alcohol (0.5 mmol) and Et_3N (0.05 g, 0.5 mmol) were added to the respective thiocarbonyl-6-nitrobenzotriazole **3.11a-h** dissolved in CH_2Cl_2 (30 mL) at rt. Stirring was continued overnight, then solvent was removed by rotary evaporation. The residue was redissolved in EtOAc (100 mL), washed with 5% Na_2CO_3 solution (3 x 100 mL), 1M HCl (2 x 100 mL), water, and brine. The collected organic layers were dried with Na_2SO_4, and the solvent was removed under vacuum. Recrystallization from EtOAc/ hexanes afforded thionoesters **3.12a–c**.

***O*-Naphth-1-yl 4-methoxythiobenzoate (3.12a).** Yellow needles (88%), mp 93–95 ^oC. ^1H NMR δ 3.91 (s, 3H), 6.98 (d, *J* = 9.0 Hz, 2H), 7.24–7.27 (m, 1H), 7.44–7.56 (m, 3H), 7.80 (t, *J* = 6.3 Hz, 2H), 7.90 (d, *J* = 7.8 Hz, 1H), 8.49 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR δ 55.7, 113.7, 119.0, 121.6, 125.4, 126.4, 126.6, 126.8, 128.2, 131.0, 131.8, 134.8, 151.0, 164.3, 209.6. Anal. Calcd. For $C_{18}H_{14}O_2S$: C, 73.44; H, 4.79. Found: C, 72.65; H, 4.89.

***O*-Naphth-1-yl 4-nitrothiobenzoate (3.12b).** Red needles (99%), mp 139–140 ^oC. ^1H NMR δ 7.28 (d, *J* = 7.5 Hz, 1H), 7.46–7.59 (m, 3H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 8.35 (d, *J* = 9.0 Hz, 2H), 8.61 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR δ 118.6, 121.0, 123.6, 125.4, 126.1, 126.75, 126.84, 127.0, 128.4, 130.2, 134.8, 141.7, 150.4, 150.5, 207.2. Anal. Calcd. For $C_{17}H_{11}NO_3S$: C, 66.01; H, 3.58; N, 4.53. Found: C, 66.07; H, 3.47; N, 4.45.

***O*-Naphth-1-yl 2-thienylcarbothioate (3.12c).** Yellow needles (62%), mp 97–98 ^oC. ^1H NMR δ 7.08 (dd, *J* = 4.8, 3.9 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.39–7.49 (m, 3H), 7.57 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.81–7.85 (m, 2H), 8.07 (dd, *J* = 3.9, 1.2 Hz, 1H). ^{13}C NMR δ 119.3, 121.6, 125.5, 126.8, 126.9, 128.4, 128.8, 132.9,

134.8, 135.3, 144.8, 150.3, 201.7. Anal. Calcd. For $C_{15}H_{10}OS_2$: C, 66.64; H, 3.73. Found: C, 66.23; H, 3.71.

CHAPTER 4
SYNTHESES AND CHARACTERIZATION OF ENERGETIC MATERIALS

4.1 Introduction

This chapter is a summary of work completed in collaboration with the US Army on the synthesis and characterization of energetic materials. Three projects are presented: synthesis and characterization of (i) blowing agents, (ii) hypergolic agents and (iii) dinitro substituted five-membered heterocycles.

4.1.1 Synthesis and Characterization of Blowing Agents

The rubber industry employs blowing agents (gas generating agents), such as dinitropentamethylenetetramine and *p*-tolysulfonylhydrazide, in the production of microcellular rubber.[37] Azodicarbonamide, Exocerol 232, and Hyderocerol BIH are blowing agents that are now commonly used in the plastics industry replacing CFCs to produce polymer foams.[38-40] Another significant application of blowing agents is their use in propellant formulations.[40-43]

In a collaborative effort with the US Army, development of novel munition formulations was investigated. This sub-section details the synthesis and characterization of energetic compounds to provide new blowing agents. The US Army has previously applied blowing agents (e.g. 2,4-dinitrophenylhydrazine) as energetic material additives in explosive mixtures to modify general munition properties. Inclusion of blowing agents that display separate isotherms from the other components in the explosive mixture is a method of tempering the violence of the explosion. For a particular Army formulation containing trinitrotoluene (TNT) and cyclotrimethylenetrinitramine (RDX), inclusion of

blowing agents possessing a DSC of ~180 °C provides a means of bursting open any confinement before the reaction of the main constituents, thus mitigating cook off violence.

Of particular interest are blowing agents with the following characteristics: quick generation of gas, mp higher than 75 °C, stable, and with DSC analysis that indicates gas evolution at 140–200 °C. Stable blowing agents **4.1–4.4** (utilized in the plastics and rubber industry) are reported to possess the required melting points and suitable DSCs (Figure 4-1) .[39, 84-87]

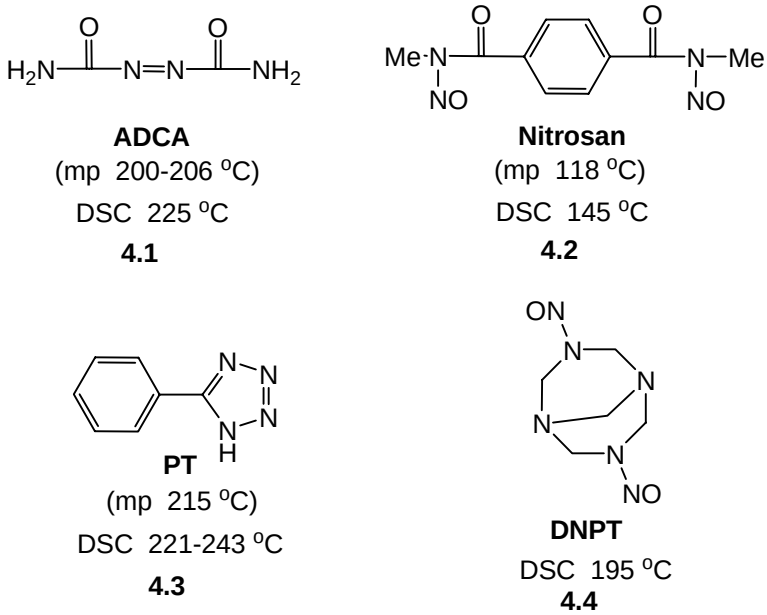


Figure 4-1. Blowing agents with reported melting points and DSCs.

The literature reports syntheses of other energetic additives **4.5–4.7** that possess measurable melting points, but have not been analyzed by TGA analysis (Figure 4-2).[88] To obtain TGA data for the evaluation of energetic additives **4.5–4.7** as blowing agents, development of reasonable syntheses that could potentially be scaled up to provide 50–100 g quantities of these compounds was undertaken. Pyrazolium nitrate **4.8** was an accidental discovery in that it was a byproduct in the attempted synthesis of 3,4-

dinitropyrazole. The nitrate salt of pyrazole was easily obtained from the reaction mixture by recrystallization. This compound was also thought to be a good blowing agent candidate so testing was conducted on this nitrate salt.

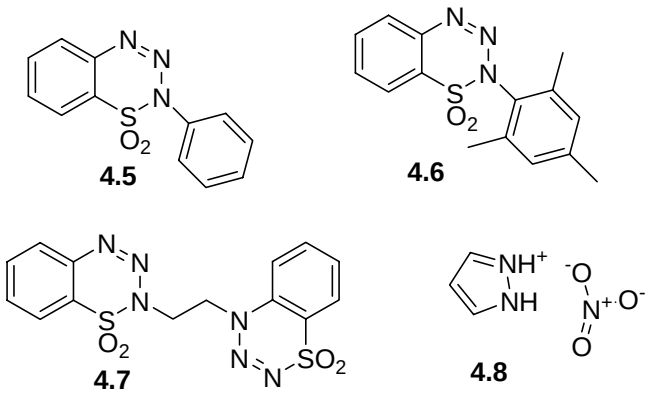


Figure 4-2. Energetic Additives without reported TGA analysis.

4.1.2 Syntheses of Hypergolic Agents

Hypergolic agents are compounds that can be used as fuels and oxidizers which ignite on contact with one another and therefore do not need a source of ignition.[44] These agents have found many uses in rocketry for both manned and unmanned space flight, mainly due to their easy start and restart capability.[44] Hypergolic propellants have advantages over other propellants such as cryogenics in that they are easily stored and are relatively inert until they are in contact with the other agent.[45] Since hypergolic propellants do not need an ignition source they are often the propellant of choice for spacecraft and satellites as they are required to stop and start their engines thousands of times over the design life of the vehicle, thereby eliminating one source of possible failure.[45]

Hypergolic compounds are employed in liquid bipropellant rocket propulsion systems which consist of gas generators, separate tanks for the storage of the hypergolic fuel and oxidizer, and lastly the engine. Operation of the propulsion system begins when

the gas generators have been initiated and the gases from the gas generator pressurize the fuel tanks. When the oxidizer and fuel valves open, the pressurized oxidizer and fuel tanks force the propellants through the plumbing and into the engine. Upon contact with one another the hypergolic fuel and oxidant spontaneously combust through an oxidation reaction thereby creating propulsion without an ignition source.[97]

The most common hypergolic fuels currently in use by various space agencies (USA, Russia and China) are hydrazine, monomethyl hydrazine (MMH) and unsymmetrical dimethyl hydrazine (UDMH).[98] The most common oxidizers are nitrogen tetroxide, inhibited fuming red nitric acid (IRFNA), nitric acid, chlorine trifluoride, and concentrated hydrogen peroxide.[99] Monomethyl hydrazine MMH and nitrogen tetroxide were used in the core liquid propellant stages of the Titan family of launch vehicles and on the second stage of the Delta rocket. The Space Shuttle orbiter uses hypergolic agents in its Orbital Maneuvering Subsystem (OMS) for orbital insertion, major orbital maneuvers and deorbit.[89] Inhibited red fuming nitric acid (IRFNA) type III B, monomethyl hydrazine (MMH) are currently the most common oxidizers for use in bipropellant rocket propulsion systems.[99]

Traditional hypergolic propellants, such as IRFNA, nitrogen tetroxide, and members of the hydrazine family are very energetic, but also toxic and/or carcinogenic. Due to these hazards, such propellants are dangerous to people, they are also expensive and hazardous to transport, handle and use. As such, there has been a desire to find non-toxic hypergolic fuels. The US Army is conducting research on suitable replacements for MMH and its derivatives by conducting thermal analysis on various tertiary diamines.

In a collaborative effort with the US Army, research was conducted to develop reasonable synthetic routes to the following hypergolic fuels which can potentially be scaled-up to provide 50–100 g quantities (Figure 4-3). These potential hypergolic fuels were then shipped to Picatinny arsenal for US Army engineers to conduct thermal analysis to be completed in the near future.

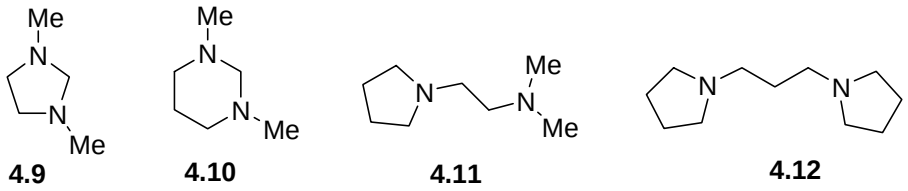
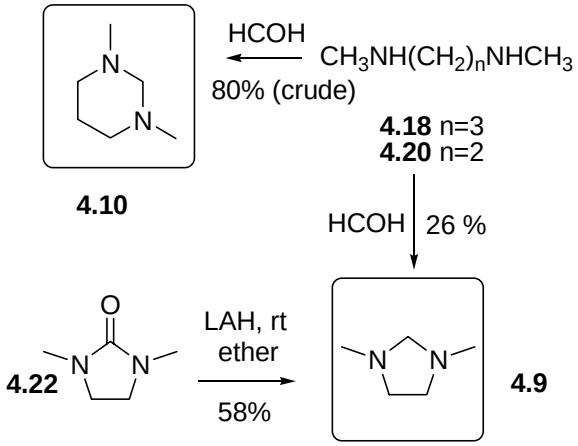


Figure 4-3. Hypergolic fuels.

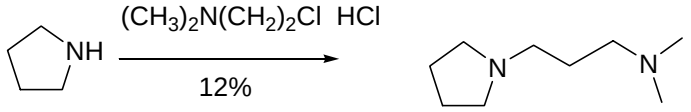
Previously 1,3-dimethylhexahydropyrimidine **4.10** and 1,3-dimethylimidazoline **4.9** were synthesized by condensation of the corresponding diamines **4.18** [90], **4.20**[91] with formaldehyde (Scheme 4-1). Stien also reported the synthesis of 1,3-dimethyl-imidazoline **4.9** by reducing 1,3-dimethylimidazolidin-2-one **4.22** with LAH at room temperature in a yield of 58 % (Scheme 4-1).[92]



Scheme 4-1. Synthesis of **4.10** and **4.9.**

Dimethyl-(2-pyrrolidin-1-yl-ethyl)amine was previously synthesized by reacting pyrrolidine with 2-chloro-*N,N*-dimethylethanamine hydrochloride to form the desired

product in only 12% yield.[95] The yield was too low to scale up to 50-100 g quantities for the US Army so a novel synthetic strategy had to be devised (Scheme 4-2).



4.11

Scheme 4-2. Synthesis of dimethyl-(2-pyrrolidin-1-yl-ethyl)amine **4.11.**

4.1.3 Synthesis of Dinitro-Substituted Five Membered Heterocycles

Dinitro derivatives of five-membered heterocycles may be of interest as energetic materials and/or possible blowing agent candidates. They have also been shown to have diverse biological activity, for example 2,4-dinitroimidazole derivatives have been shown to be very effective agents in increasing the sensitivity of hypoxic cells toward irradiation in cancer radiotherapy.[46] Numerous dinitro heterocycles have also been shown to be useful intermediates, for instance Padwa recently converted dinitrofuran to various polysubstituted phenols through S_nAr nucleophilic substitution reactions.[47]

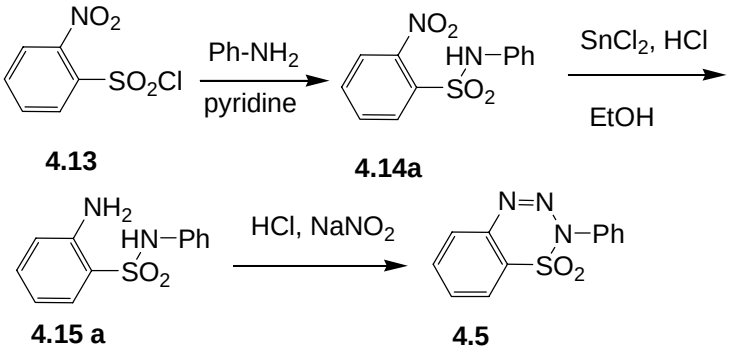
The aim of the present work is the development of reasonable syntheses of dinitro substituted five-membered heterocyclic compounds. Literature methodologies for the general preparation of dinitro substituted five-membered heterocycles are scarce. Several literature examples based on direct nitration of heterocyclic rings result in mixtures of isomers, which are often difficult to separate.[93a,b]

4.2 Results and Discussion

4.2.1 Results Syntheses and Characterization of Blowing Agents

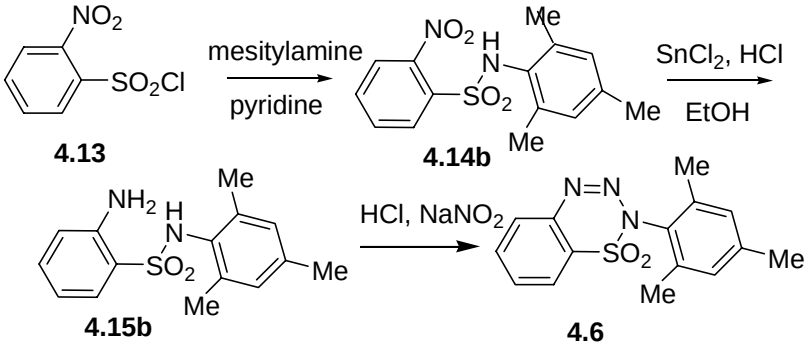
Various 2-substituted benzo[1,2,3,4]thiatriazine-1,1-dioxides 4.5-4.7 were prepared following a procedure by Ullmann et al. starting from 2-nitrosulfonyl chloride (4.13) (Schemes 4-3, 4-4, 4-5).[88]

Synthesis of 2-phenylbenzo[1,2,3,4]thiatriazine-1,1-dioxide **4.5** was carried out starting from 2-nitrosulfonyl chloride (**4.13**) (Scheme 4-3). Condensation of the sulfonyl chloride with phenylamine gave sulfonamide **4.14a** in 82 % yield. Baeyer reduction of the nitro group provided 2-amino-*N*-phenylbenzenesulfonamide (**4.15a)** in 92 % yield, which was then cyclized to 2-phenylbenzo[1,2,3,4]thiatriazine-1,1-dioxide **4.5** in 75 % yield by reaction with HONO generated in-situ.



Scheme 4-3. Synthesis of 2-phenylbenzo[1,2,3,4]thiatriazine-1,1-dioxide **4.5**.

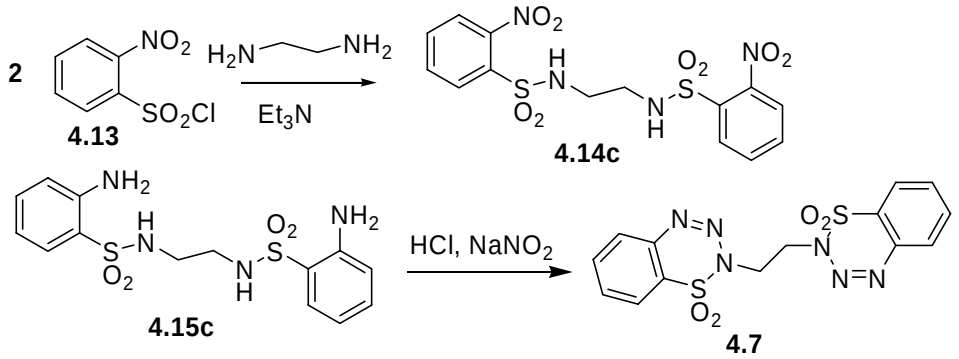
Similarly, **4.6** was prepared in 74 % yield by cyclization of **4.15b** with HONO. (Scheme 4-4). Sulfonamide **4.14b** was prepared in 70 % yield by the reaction of 2-nitrosulfonyl chloride (**4.13**) with mesitylamine.



Scheme 4-4. Synthesis of compound **4.6**.

Bis-benzo[1,2,3,4]thiatriazine-1,1-dioxide **4.7** was obtained in 68 % yield from **4**.**15c** (Scheme 4-5). Two equivalents of sulfonyl chloride **4.13** were reacted with

ethylenediamine to give sulfonamide **4.14c** in 93% yield. Upon reduction, sulfonamide **4.14c** provided **4.15c** in 92 % yield, which was cyclized with HONO to provide **4.7**.



Scheme 4-5. Synthesis of bis-benzo[1,2,3,4]thiatriazine-1,1-dioxide **4.7**.

TGA analysis (50°C to 300 °C, rate: 20 °C/min.) of benzo[1,2,3,4]thiatriazine-1,1-dioxides (**4.5**, 1.545 mg; **4.6**, 0.783 mg; **4.7**, 0.345 mg) showed a trend of gradual decomposition (Figure 4-4). 2-Phenylbenzo[1,2,3,4]thiatriazine-1,1-dioxide **4.5** showed the sharpest loss in mass, losing 30% from 210 °C to 265 °C. While **4.7** steadily decomposed, **4.6** decomposed in stages starting from 100 °C with plateaus from 110–130 °C and 140–190 °C. Compound **4.5** is the most promising among this series (**4.5-4.7**), since it demonstrated the sharpest decomposition.

Unfortunately it was found that upon storing at room temperature for extended periods of time compounds **4.5-4.7** decomposed into complex mixtures. Since blowing agents must be stored in munitions casings under diverse temperature ranges these compounds would be of no use a energetic additives.

Originally pyrazolium nitrate **4.8** was formed as a byproduct in the attempted dinitration of pyrazole from a previous route established in the Katritzky group.[94] Upon adding ethyl acetate to the reaction mixture it was found that small microcrystals formed, and NMR, CHN analysis and X-ray crystallography showed that the byproduct was pyrazolium nitrate. Unfortunately it was also found that the reaction between pyrazole

4.16 and concentrated nitric acid in trifluoroacetic anhydride gave an inter-chelating molecular complex of 4-nitropyrazole and oxalic acid **4.17** not 3,4-dinitropyrazole (Scheme 4-6).

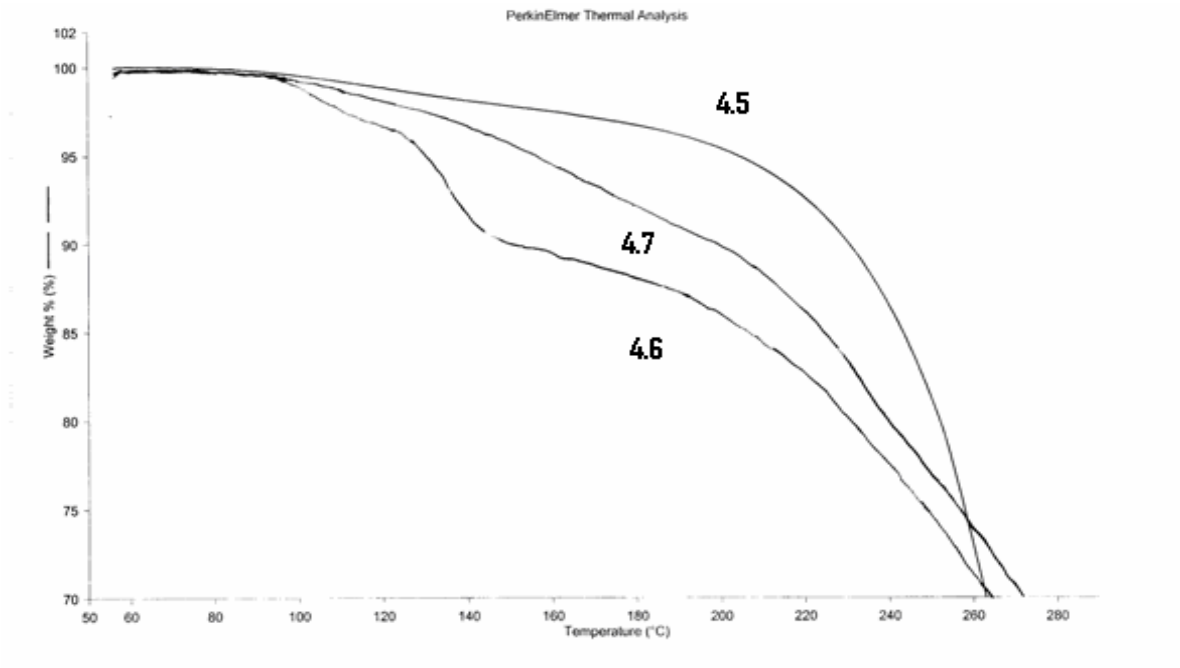
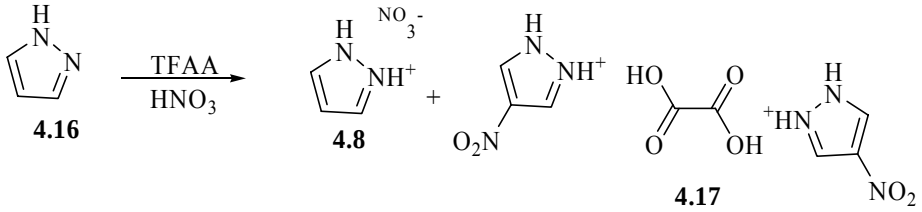


Figure 4-4. TG_A analysis of compounds **4.5-4.7.**



Scheme 4-6. Synthesis of inter-chelating molecular complex of 4-nitropyrazole and oxalic acid **4.17**.

This result is consistent with CHN data (Calcd for $C_8H_8N_6O_8$: C, 30.39; H, 2.55; N, 26.58. Found: C, 30.54, H, 2.72; N, 30.85), and X-ray analysis which shows that the structure is a complex of 2 molecules of 4-nitropyrazole and 1 molecule of oxalic acid (Figure 4-5). It is believed that oxalic acid arises from the hydrolysis of trifluoroacetic acid.

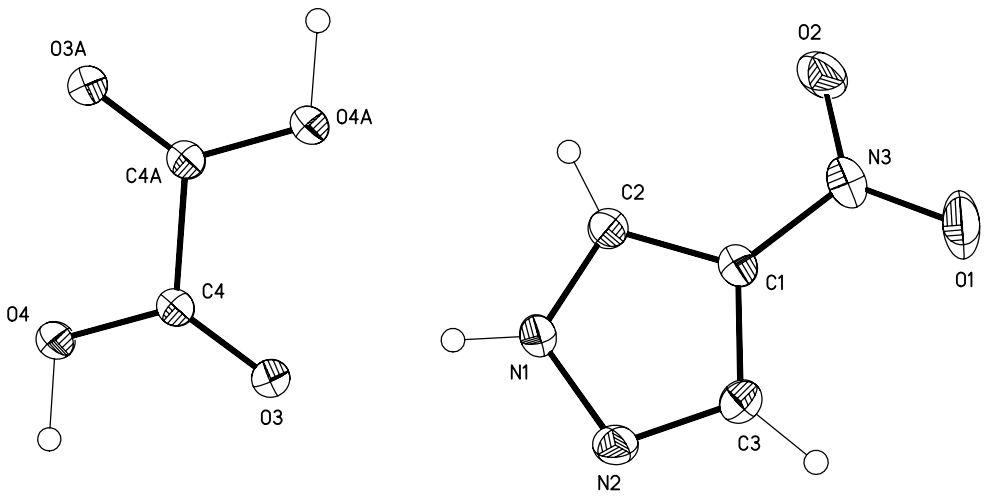


Figure 4-5. X-ray of molecular complex of 4-nitropyrazole and oxalic acid **4.17**.

While this result was not expected it was believed that pyrazolium nitrate could be a viable blowing agent candidate.

TGA analysis of 1.4052 mg of the pyrazolium nitrate **4.8** showed a decline in mass before 160 °C. Thus it is not a good candidate for the specifications of a blowing agent, although it may be suitable for other Army applications (Figure 4-6). The calculated heat flow for the nitrate salt is +0.35 W/mmol.

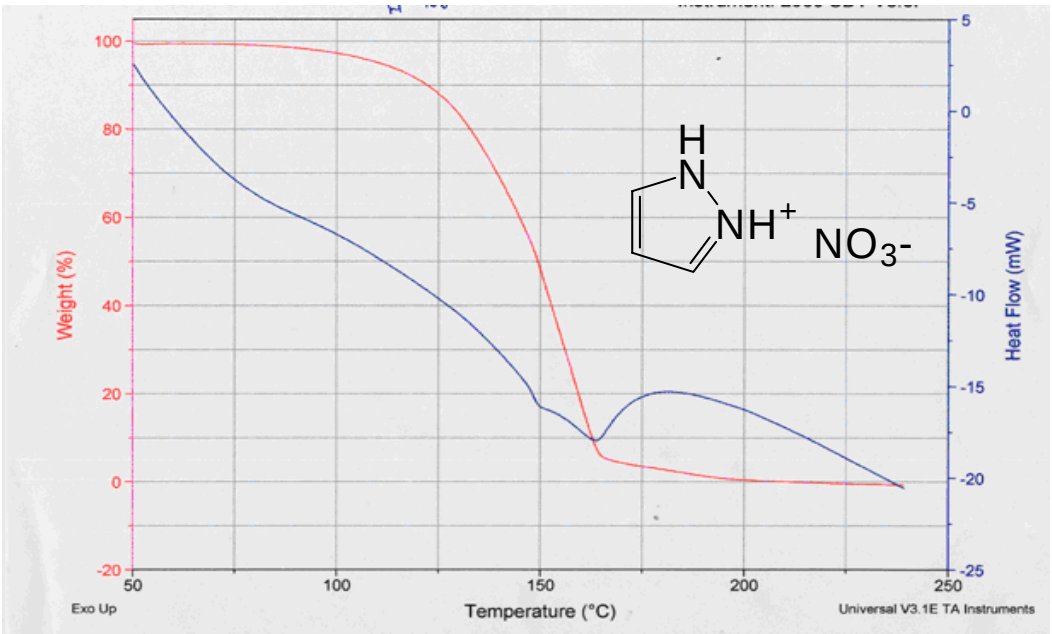
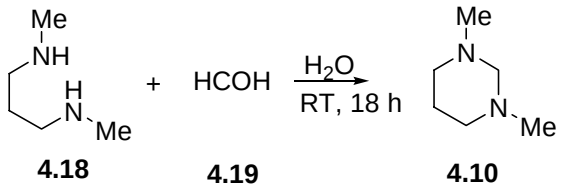


Figure 4-6. TGA and DSC analysis of pyrazolium nitrate **4.8.**

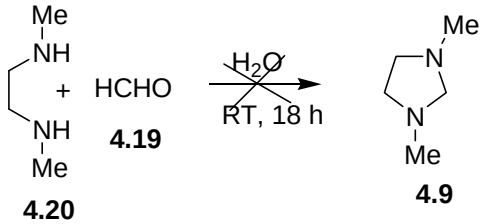
4.2.2 Results Synthesis of Hypergolic Agents

The first attempted synthesis of 1,3-dimethylhexahydropyrimidine **4.10** was achieved in 72% yield by the treatment of *N*-methyl-*N*-[3-(methylamino)propyl]amine **4.18** with formaldehyde **4.19** in water at room temperature for 18 h (Scheme 4-7).



Scheme 4-7. Synthesis of cyclic aminal **4.10** from formaldehyde.

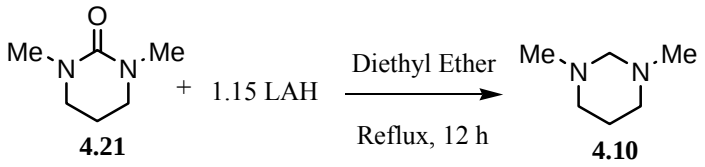
While this methodology worked well it used the relatively expensive reagent *N*-methyl-*N*-[3-(methylamino)propyl]amine. These reaction conditions also failed to produce 1,3-dimethyl-imidazoline **4.9** when *N,N*-dimethylethane-1,2-diamine **4.20** was reacted with formaldehyde **4.19** (Scheme 4-8).



Scheme 4-8. Synthesis of cyclic aminal **4.9** from formaldehyde.

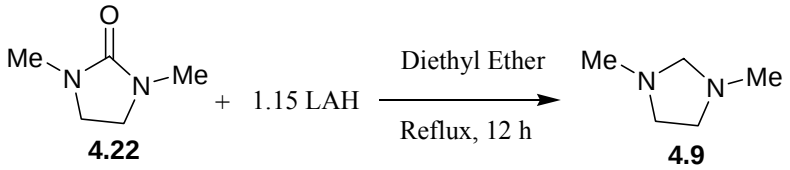
Another methodology for the preparation of 1,3-dimethylhexahydropyrimidine **4.10** by the reduction of 1,3-dimethyltetrahydropyrimidin-2-one **4.21** with 1.15 equivalents of LAH in ether under reflux for 12 h afforded a 99 % yield. This provided a cheap source of starting material (1,3-dimethyltetrahydropyrimidin-2-one **4.21**) and better conditions for isolation of the desired product by simply evaporating ether under reduced pressure (Scheme 4-9). The conditions established by Johannes and Turid in which the cyclic urea **4.21** was reduced with LAH at room temperature gave a complex mixture, perhaps

because LAH oxidized before the reaction could take place or it was not soluble enough at room temperature.[90]



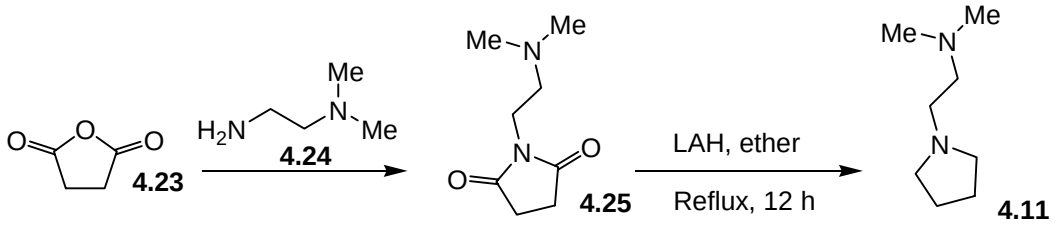
Scheme 4-9. Synthesis of cyclic aminal **4.10** via reduction with LAH.

This methodology also reduced 1,3-dimethylimidazolidin-2-one **4.22** into 1,3-dimethyl imidazoline **4.9** in 80% yield (Scheme 4-10).



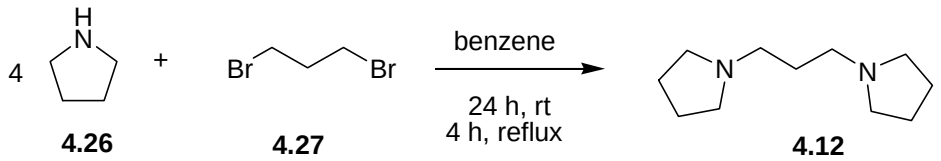
Scheme 4-10. Synthesis of cyclic aminal **4.9** via reduction with LAH.

N,N-Dimethyl-2-(1-pyrrolidinyl)-1-ethanamine **4.11** was obtained by the reaction of 2.3 equivalents of LAH and 1-[2-(dimethylamino)ethyl]dihydro-1*H*-pyrrole-2,5-dione **4.25** in ether under reflux for 12 h in 87 % yield. Intermediate **4.25** was prepared by treatment of succinic anhydride **4.23** with dimethylaminoethylamine **4.24** in a microwave synthesizer at 100 watts and 130 ^{o}C for 5 minutes followed by distillation to give the product **4.25** in 39 % yield (Scheme 4-11). This methodology was superior to the previous literature method established by Ried who reacted pyrrolidine with 2-chloro-*N,N*-dimethylethanamine hydrochloride to obtain only a 12% yield.[95]



Scheme 4-11. Synthesis of *N,N*-dimethyl-2-(1-pyrrolidinyl)-1-ethanamine **4.11**.

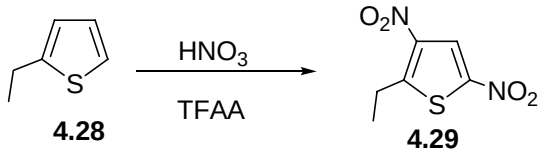
1,3-(Dipyrrolidyl)propane **4.12** was prepared in 43% yield by the reaction of 4 equivalents pyrrolidine **4.26** with 1,3-dibromopropane **4.27** using a procedure by Gero (Scheme 4-12).[96]



Scheme 4-12. Synthesis of 1,3-(dipyrrolidyl)propane **4.12.**

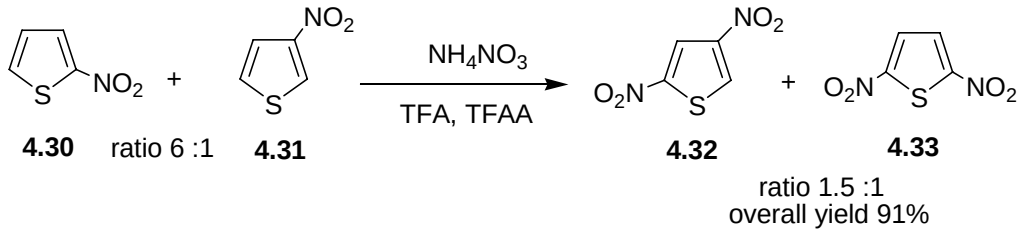
4.2.3 Results Nitration of Five Membered Heterocycles

The direct dinitration of 2-ethylthiophene **4.28** was accomplished with HNO_3 in TFAA at 0 ^{o}C for 12 h. It was found that this reaction proceeds regioselectively to the desired dinitro derivative **4.29** in a yield of 37% (Scheme 4-13).



Scheme 4-13. Synthesis of 2-ethyl-3,5-dinitrothiophene **4.29**.

Attempts to extend the standard reaction conditions for dinitration of 2-bromothiophene gave a complicated mixture of nitro substituted derivatives. The commercially available mixture of 2- and 3-mononitrothiophenes **4.30-4.31** was reacted with ammonium nitrate in trifluoroacetic anhydride at room temperature for 16 h to yield a mixture of 2,4- **4.32** and 2,5-dinitrothiophenes **4.33** in high yield (91%). Analysis of the ^{1}H NMR spectra for the mixture showed a singlet at δ 7.27 which is characteristic for 2,5-dinitrothiophene and a doublet of doublets characteristic for 2,4-dinitrothiophene at δ 8.44. Integration of these two peaks gave a ratio of 1.5:1 for 2,4-dinitrothiophene and 2,5-dinitrothiophene. The mixture melts at 53.1-54.0 ^{o}C and might be a good candidate as an energetic additive (Scheme 4-14).



Scheme 4-14. Synthesis of mixture of 2,4- **4.32** and 2,5-dinitrothiophenes **4.33.**

4.3 Conclusion

This chapter summarizes the work accomplished in collaboration with the US Army on the synthesis and characterization of broadly defined energetic materials. The work on blowing agents included thermogravimetric analysis in order to gauge their usefulness as blowing agents, unfortunately none of the synthesized agents were applicable as blowing agents due to either being unstable at room temperature **4.5-4.7** or undergoing undesirable thermal decomposition profiles **4.8**. Four hypergolic compounds **4.9-4.12** were synthesized and the methodologies used for compounds **4.9-4.11** improved upon the previous literature methods by providing higher yields and easier isolation of the compounds. Dinitration of five membered rings is preliminary work but the two examples listed have the advantage of being simple, one step procedures with yields ranging from moderate to excellent. More examples of di-nitrosubstituted five membered heterocycles are planned for synthetic study in the future.

4.4 Experimental

Caution! Although we have not experienced any problems in synthesizing or handling these compounds, proper safety precautions should be followed and these materials should be treated with extreme care.

Melting points were determined using a Bristoline hot-stage microscope and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a 300

MHz NMR spectrometer in DMSO-d_6 or chloroform-*d* solution as indicated. THF was distilled from sodium-benzophenone ketal prior to use. Column chromatography was performed on silica gel (300–400 mesh). Elemental analyses were performed on a Carlo Erba-1106 instrument. For the DSC and TGA experiments a Perkin Elmer DSC 7 or Perkin-Elmer TGA 7 were used to analyze samples (~3 mg) with a heating rate of 10 or 20 ^{o}C/min in an argon atmosphear with a flow rate of 50 mL/min. Thermal calibrations for differential scanning calorimetry were made using indium and freshly distilled *n*-octane as references. Heats of fusion were referenced against indium.

4.4.1 General Procedure for the Preparation of Benzo[1,2,3,4]thiatriazine-1,1-dioxides 4.5-4.6

Sodium nitrite (0.36 g, 5.2 mmol) was added to a stirred solution of the corresponding sulfonamide (3.5 mmol) dissolved by gentle warming in aqueous acetic acid 95% (50 mL) and then cooled to 25 ^{o}C. The resulting mixture was stirred at 25 ^{o}C for 8 hours, then ice-cold water (200 mL) was added and the precipitated product was filtered and washed with water. The red solid was dried *in vacuo* overnight to afford a 75% yield of 2-phenyl-2*H*-benzo[1,2,3,4]thiatriazine-1,1-dioxide and 74% of 2-(2,4,6-Trimethyl-phenyl)-2H-benzo[1,2,3,4]thiatriazine-1,1-dioxide.

2-Phenyl-2*H*-benzo[1,2,3,4]thiatriazine-1,1-dioxide (4.5) Red microcrystals (75%) mp 101.0^{o}C, (Lit. mp 111 ^{o}C).[52] ^{1}H NMR δ 7.98–8.03 (m, 2H), 7.54–7.59 (m, 1H), 7.39–7.44 (m, 1H), 7.29–7.34 (m, 1H), 7.03–7.25 (m, 3H).^{13}C NMR δ 135.5, 132.5, 128.4, 130.4, 129.1, 125.4, 125.3, 125.0, 122.1, 120.6.

2-(2,4,6-Trimethylphenyl)-2*H*-benzo[1,2,3,4]thiatriazine-1,1-dioxide (4.6) Red microcrystals (74%) mp 151.0 ^{o}C, (Lit. mp 150 ^{o}C).[52] ^{1}H NMR δ 8.09–8.14 (m, 1H),

7.91–7.96 (m, 1H), 7.80–7.86 (m, 1H), 2.35 (s, 3H), 2.29 (s, 6H). ^{13}C NMR δ 141.5, 140.7, 138.9, 134.0, 132.8, 130.3, 129.8, 127.7, 129.6, 120.6, 21.1, 18.3.

4.4.2 General Procedure for the Preparation of Pyrazolium Nitrate 4.8

Trifluoroacetic anhydride [6.5 mL] was added to 1-H pyrazole [0.68 g,10 mmol] under vacuum and chilled in an ice bath. Concentrated nitric acid [2.2 mL] was added 0.5 mL increments very slowly (~45 minutes) to the mixture. After stirring for 12 h at room temperature, ethyl acetate (50 mL) was added to the reaction mixture and then stored in freezer 3 hours until the byproduct precipitated out as white crystals which were then filtered off. Note: this was step was repeated as necessary until no byproduct was evident after freezing the mixture. (0.65 g, Yield=50%) precipitated off as white microcrystals.

Pyrazolium nitrate (4.8) White microcrystals (50%). ^{1}H NMR δ 8.59 (s, 1H), 12.21 (s, 1H). ^{13}C NMR δ 32.5, 134.1, 135.5.

4.4.2.1 General Procedure for the Preparation of Hypergolic Aminals 4.9 and 4.10.

The corresponding cyclic urea (16.8 mmol) was added dropwise to a solution of LAH (0.80g, 19.2 mmol) in diethyl ether (160 mL). The mixture was then refluxed gently for 12 hr. Water (5mL) was added slowly then 2N NaOH (2mL) solution was added dropwise to quench the reaction. The solid was then filtered off and diethyl ether was removed under reduced vacuum to afford 1,3-dimethylimidazolidine (1.46 g) in a yield of 80% and 1,3-dimethylhexahydropyrimidine (1.91 g) in a yield of 99%.

1,3-Dimethylimidazolidine (4.9) Clear oil (80%) bp 111 ^{o}C/760 mm Hg, (lit bp 110 ^{o}C/760 mm Hg).[57] ^{1}H NMR δ 2.25 (s, 6H), 2.63 (s, 4H), 3.15 (s, 2H). ^{13}C NMR δ 41.5, 54.3, 79.8.

1,3-Dimethylhexahydropyrimidine (4.10) Clear oil (99%) bp 131 ^{o}C/760 mm Hg, (lit bp 126 ^{o}C/760 mm Hg).[56] ^{1}H NMR δ1.69 (m, 2H), 2.24 (s, 6H), 2.40-2.43 (m, 4H), 2.97 (br s, 2H). ^{13}C NMR δ 23.9, 43.1, 54.1, 79.6

4.4.2.2 General Procedure for the Preparation of Hypergolic Agent Dimethyl(2-pyrrolidin-1-yl-ethyl)amine 4.11

1-(2-Dimethylaminoethyl)pyrrolidine-2,5-dione (4g, 23.5 mmol) was added to a solution of LAH (2.04g, 54.05 mmol) in ether. The mixture was refluxed overnight under nitrogen then the mixture was quenched with water and the organic layer was filtered off. Ether was removed under reduced pressure to afford dimethyl-(2-pyrrolidin-1-yl-ethyl)amine (2.91 g) in a yield of 87%.

***N,N*-Dimethyl-2-(1-pyrrolidinyl)-1-ethanamine (4.11)** Clear oil (87%) bp 170.9 ^{o}C/760 mm Hg, (lit bp 56.5 ^{o}C/1.5 mm Hg).[64] ^{1}H NMR δ1.70-1.74 (m, 4H), 2.19 (s, 6H), 2.35-2.40 (m, 2H), 2.47-2.54 (m, 6H). ^{13}C NMR δ 21.4, 43.9, 52.32, 52.34, 56.5.

4.4.2.3 General Procedure for the Preparation of Hypergolic Agent 1,3-(Dipyrrolidyl)propane 4.12

To a solution of 1,3-dibromopropane (8.35 mL, 21 mmol) and dry benzene (200 mL) was added pyrrolidine (27.02 mL, 84 mmol). The reaction mixture was stirred at room temperature for 12 hours then the mixture was refluxed for 4 hours on a hot water bath, cooled and filtered from pyrrolidine bromide. Benzene was removed under reduced vacuum to afford 1,1'-(1,3-propanediyl)bis-pyrrolidine (6.5g, 43% yield).

1,3-(dipyrrolidyl)propane (4.12) Clear oil (43%) bp 111°C/760 mm Hg, (lit bp 110 ^{o}C/760 mm Hg).[65] ^{1}H NMR δ1.70-1.70 (m, 10H), 2.45-2.50 (m, 12H). ^{13}C NMR δ 23.5, 28.8, 54.4, 55.0.

4.4.3 General Procedure for the Preparation of 2-Ethyl-3,5-Dinitrothiophene 4.29

Trifluoroacetic anhydride (2.9 mL) was added to 2-ethylthiophene (0.56 mL, 5 mmol) under vacuum and chilled in an ice bath. Concentrated nitric acid (0.88 mL) was added in 0.3 mL increments very slowly (~45 minutes) to the mixture. After stirring for 12 h at room temperature, ethyl acetate (50 mL) was added to the reaction mixture and the organic layer was washed with brine and the organic layer was extracted. Purification by column chromatography gave 2-ethyl-3,5-dinitrothiophene (0.29 g, 37% yield) as a red oil.

2-Ethyl-3,5-dinitrothiophene (4.29) Red oil (37%). ^{1}H NMR δ 1.48 (t, J=7.5 Hz, 3H), 3.39 (dd, J=7.5 Hz, 2H), 8.36 (s, 1H). ^{13}C NMR δ 13.8, 23.8, 124.5, 141.3, 145.4, 157.4. Anal. Calcd for $C_6H_6N_2O_4S$: C 35.64, H2.99, N 13.86. Found C 35.82, H 2.83, N 13.57.

4.4.4 General Procedure for the Preparation of 2,4-Dinitrothiophene 4.32, 2,5-Dinitrothiophene 3.33

Pure 2-nitrothiophene (0.5g, 3.9 mmol) was added dropwise to a solution of NH_4NO_3 (0.62g, 3.9 mmol) in TFA (1.2 mL) and TFAA (1.1 mL) at 0 ^{o}C. The reaction mixture was allowed to warm to room temperature and was stirred for 12 hr. Water was added to the reaction mixture and the product was filtered off with gravity filtration to give a mixture of 2,4-dinitrothiophene and 2,5-dinitrothiophene (0.94 g, 91%).

2,4-dinitrothiophene (4.32), 2,5-dinitrothiophene (4.33) (mp 53.1-54.0 ^{o}C) ^{1}H NMR δ 7.27 (s, 1H), 7.87 (s, 1H), 8.44 (dd, J1=1.8, 10.5 Hz, 1H). Anal. Calcd for $C_4H_2N_2O_4$: C 27.59, H 1.16, N 16.09. Found C 28.02, H 0.96, N 15.68.

CHAPTER 5
CONCLUSION

The successful application of 1-benzotriazolyl-2-propynones as a novel 1-3-biselectrophile was demonstrated in Chapter 2. 1-Benzotriazolyl-2-propynones, in comparison with the literature procedures to synthesize pyrido[1,2-*a*]pyrimidin-2-ones, offered shorter reaction times, cleaner conversion to products, and higher yields. 1-Benzotriazolyl-2-propynones were also successfully reacted with other 1,3-bis-nucleophiles: 2-picolines, 2-methylquinoline and 2-aminothiazole to form 2*H*-quinolizin-2-ones, pyrido[1,2-*a*]quinolin-3-ones, and thiazolo[3,2-*a*]pyrimidin-7-one in moderate to excellent yields.

Several novel thioacyl nitrobenzotriazoles, which were synthesized from a previous procedure from Rapoport, were shown to be effective thioacylating reagents and a viable alternative to previous problematic routes. This procedure was compared in conjunction with another procedure which used a Grignard methodology for the synthesis of thioacyl benzotrizoles. It was found that the Grignard method is the preferred means of obtaining arylthiocarbonylbenzotriazoles, while Rapoport's synthesis is preferred for alkyl, alkynyl, and heteroaryl thiocarbonylbenzotriazoles. To test the thioacylating ability of the new thioacyl nitrobenzotriazoles synthesized, several were reacted with 1-naphthalenol to form novel thionoesters. Advantages of thioacyl nitrobenzotriazoles are that they circumvent the use of unstable or hazardous reagents, the mild conditions employed are tolerable of a large variety of functional groups and yields are comparable and in many cases higher than previously reported methods.

Chapter 4 summarizes the work accomplished in collaboration with the US Army on the synthesis and characterization of broadly defined energetic materials. The work on blowing agents included thermogravimetric analysis in order to gauge their usefulness as blowing agents, unfortunately none of the synthesized agents were applicable as blowing agents, due to either being unstable at room temperature or undergoing undesirable thermal decomposition profiles. Four hypergolic compounds were synthesized and the methodologies used for three of the compounds improved upon the previous literature methods by providing higher yields and easier isolation of the compounds. Dinitration of five-membered rings is preliminary work, but the two examples listed have the advantage of being simple, one-step procedures with yields ranging from moderate to excellent. More examples of dinitrosubstituted five-membered heterocycles are planned for synthetic study in the future

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BIOGRAPHICAL SKETCH

James William Rogers was born in Sandwhich, Illinois, on October 3rd, 1976, to William Edward Rogers and Barbara Jean Rogers. Shortly after birth, the family moved to Aurora, Illinois, where they lived for four years. The family then moved to Phoenix, Arizona, for 2 years, and then moved back to the Midwest to Granite City, Illinois, which is close to St. Louis, Missouri. William Rogers supported the family by working as a chemist at Sigma-Aldrich. James Rogers graduated from Granite City Senior High School in 1995; he lettered varsity in football but academic honors so far eluded him. James went to college at nearby Southern Illinois University at Edwardsville in the fall term of 1995. He paid all of his education expenses by working as a waiter at The Lawyers Club of St. Louis. After receiving a Bachelor of Science in chemistry at age 23, James began work at Abbott Labs in North Chicago, Illinois, as a QC chemist. After four months the chemistry department at Southern Illinois called with an offer for admission to graduate school. He refused at first but after a week of thought decided to enroll and resigned his position at Abbott Labs. James enrolled in the graduate program at Southern Illinois in the summer of 2000, working under the tutelage of Professor Tim Patrick, whose novel research inspired James to continue his education. He received a Master of Science in chemistry in August of 2002, this time he graduated with high honors and received an award for outstanding chemical research. James also met his future wife Hong Yu at Southern Illinois, who also received a Master of Science in chemistry in the summer of 2002. In the summer of 2002, Hong and James began their PhD study at the

University of Florida and were married in 2003. James now works under the mentorship of Professor Alan Katritzky. On May 22nd, 2005, at 6 AM James and Hong were blessed by the birth of their daughter, Elaine Yu Rogers.