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Hexa-aryl/alkylsubstituted Cyclopropanes

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SYNTHESIS OF HEXA-ARYL/ALKYLSUBSTITUTED CYCLOPROPANES

by

PHONG MINH TRUONG

Under the Direction of Davon G. Kennedy

ABSTRACT

A series of penta-aryl/alkyl-1-(toluene-4-sulfonyl)-4,5-dihydro-1H-pyrazole **5a-c** was synthesized by addition of methyllithium or phenyllithium followed by trapping the nitrogen anion intermediate with tosyl-fluoride to cyclic azines **2a,b**. Addition of methyllithium or phenyllithium to **5a-c** generated a series of hexa-aryl/alkylsubstituted-4,5-dihydro-3*H*-pyrazoles **6a-c**. Neat thermolysis of hexa-aryl/alkylsubstituted-4,5-dihydro-3*H*-pyrazoles **6a-c** at 200°C produced hexa-aryl/alkylsubstituted cyclopropanes **7a-c** in high yield.

INDEX WORDS: Hexasubstituted Cyclopropanes, Thermolysis, Pyrazoles, Tosyl-halide, Alkylithium .

SYNTHESIS OF HEXA-ARYL/ALKYLSUBSTITUTED CYCLOPROPANES

by

PHONG MINH TRUONG

A Thesis Submitted in Partial Fulfillment of Requirements for the Degree of

Master of Science

in the College of Arts and Sciences

Georgia State University

2005

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2005

SYNTHESIS OF HEXA-ARYL/ALKYLSUBSTITUTED CYCLOPROPANES

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Georgia State University
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LIST OF ABBREVEATIONS

THF	Tetrahydrofuran
TMS	Tetramethylsilane
Ts-F	p-toluenesulfonylfluoride
Ts-Cl	p-toluenesulfonylchloride
MeI	Iodomethane
H ₂ NNH ₂	hydrazine
MeLi	Methyl lithium
PhLi	Phenyl lithium
CDCl ₃	Deuterated chloroform
rt	Room temperature
mp	Melting point
S _N 2	Substitution nucleophilic bimolecular
NMR	Nuclear magnetic resonance
IR	Infra red spectroscopy
GC	Gas chromatography
GC/MS	Gas chromatography mass spectrometer

Chapter 1

Introduction

There has been extensive research on the synthesis of cyclopropanes over the years and several standard methods have been developed. However, most of these methods work well only for tetrasubstituted-cyclopropanes or less substituted-cyclopropanes. Pentasubstituted-cyclopropanes are very difficult to synthesize, and hexasubstituted-cyclopropanes are almost unknown. For example, only two hexa-aryl/alkylsubstituted-cyclopropanes have been reported.^{1,2,3,4} One of these compounds is 1,1,2,2,3,3-hexamethyl-cyclopropane, was obtained from the low temperature decomposition of 2,4-dibromo-2,3,3,4-tetramethylpentane¹, by photolysis of hexamethylcyclohexane-1,3,5-trione², or by thermolysis of 2-methoxy-2,5,5-trimethyl- Δ^3 -1,3,4-oxadiazoline in tetramethyl ethylene³. The second compound is 1-phenyl-1,2,2,3,3-pentamethyl-cyclopropane, which was synthesized by addition of excess methyl lithium to a solution containing dichloromethyl-benzene and 2,3-dimethyl-ethylene⁴. These available methods for hexa-aryl/alkylsubstituted-cyclopropanes are very specific and limited. The goal of this research is to develop a new, general methodology to hexa-aryl/alkylsubstituted-cyclopropanes based on pyrazoline chemistry. This research potentially will help expand the synthetic work of cyclopropanes and to explore the mechanistic insight for decomposition of pyrazolines.

1. 1 Pyrazoles and Pyrazolines

Pyrazoles are five-member heterocyclic compounds containing three carbon atoms, two adjacent nitrogen atoms and two double bonds.⁵ In general, the nitrogen atoms are at position one and two in each structure.⁶ The isomers for 1*H*-pyrazole include 2*H*-pyrazole, 3*H*-pyrazole, and 4*H*-pyrazole. 1*H*, 2*H*, and 3*H* prior to the word “pyrazole” indicate the location of the first hydrogen atom or substituent that corresponds to the numbering system for the pyrazoles. The numbers in front of the word “dihydro” indicate the locations of saturated carbon (Figure 1). For dihydro-2*H* and 3*H*-pyrazoles, the compound must contain one double bond and they can be referred to as pyrazolines or dihydro-pyrazoles. In 4*H*-pyrazole, which is also known as cyclic azine or isopyrazole, the compound must contain two double bonds and one tetrahedral carbon.⁷

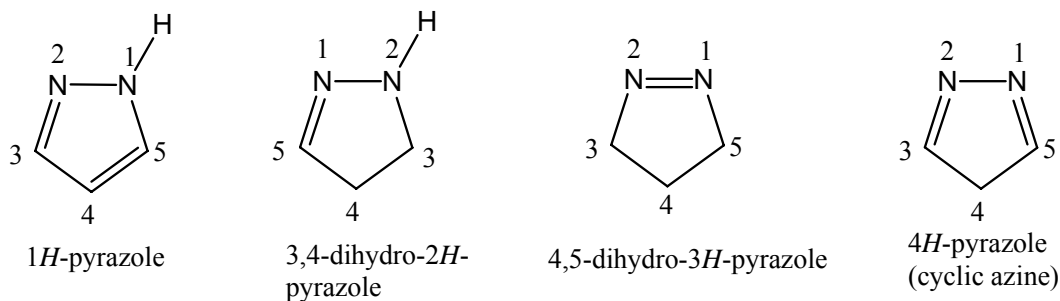
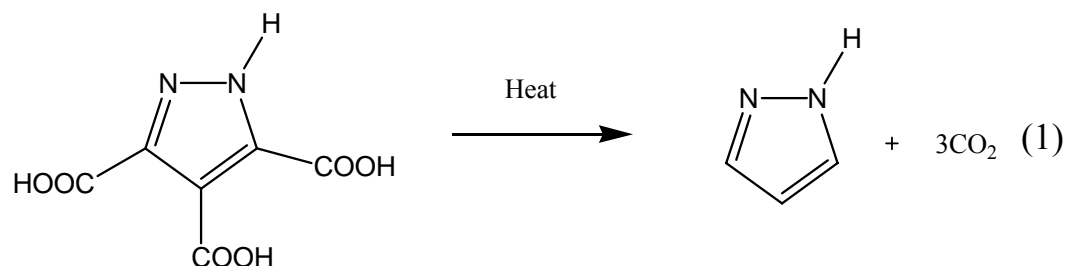


Figure 1. Naming and numbering system for isomers of 1*H*-pyrazoles.

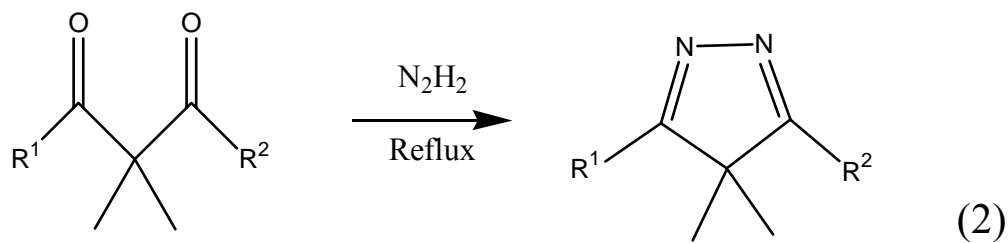
Pyrazole (1*H*-pyrazole) was first described by Knorr in 1883.⁸ However, it was first prepared by Buchner in 1889 by decarboxylation of pyrazole-3,4,5-tricarboxylic acid (1).⁹ Since then the studies of the pyrazoles have centered principally about structural problems arising from the tautomerism existing in the

N-substituted types and isomerism of the N-substituted derivatives.¹⁰ Over the years, many methods have been developed to prepare pyrazoles and their derivatives.



Reaction 1. 1H-pyrazole prepared by Buchner.

The most widely used and the most general method for pyrazole synthesis are from the reaction between β -dicarbonyl compounds and hydrazines. An example of this type of reaction would be hydrazine reacting with a series of 1,3-diketones (2).¹¹



$R^1 = \text{Ph}$, $R^2 = \text{Ph}$, 97% yield

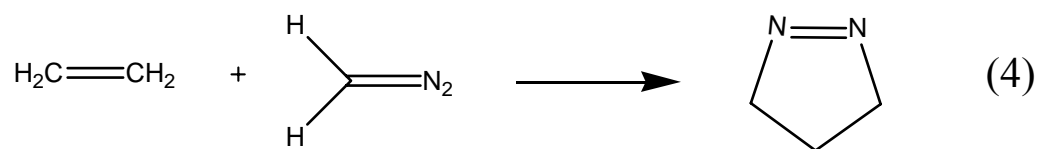
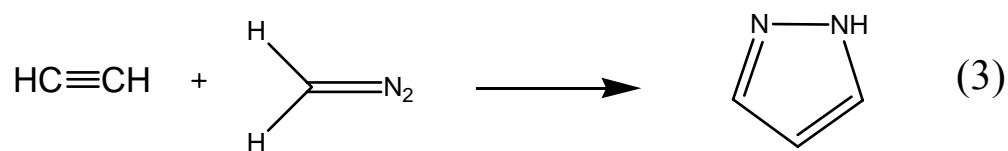
$R^1 = \text{Ph}$, $R^2 = \text{Me}$, 93% yield

$R^1 = \text{Me}$, $R^2 = \text{Me}$, 92% yield

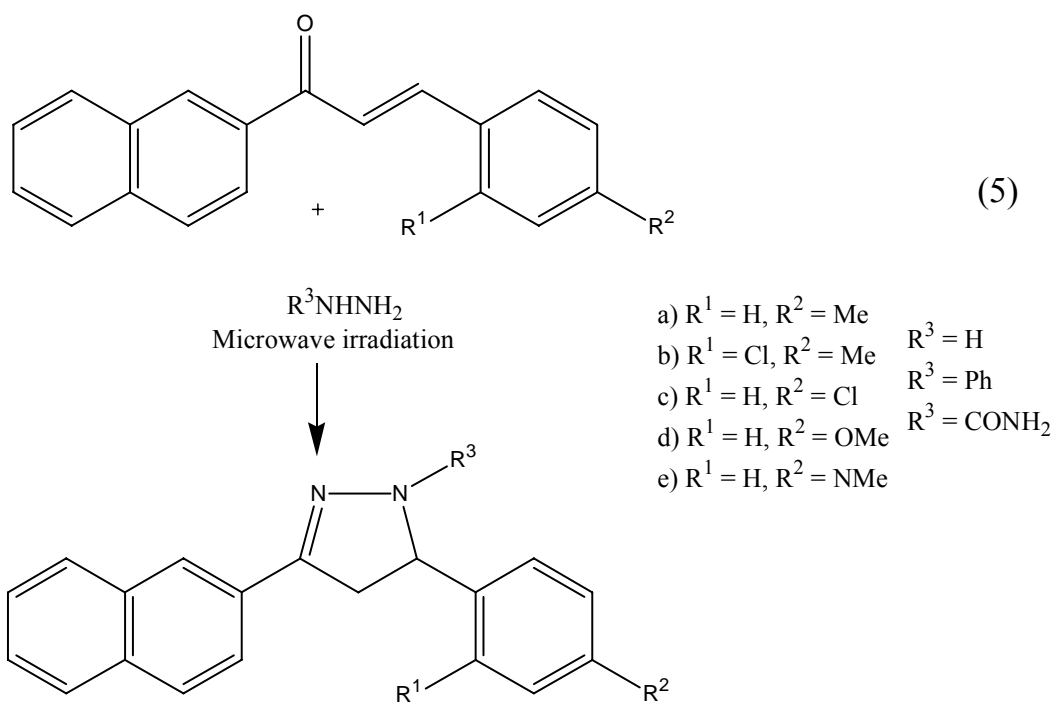
A well-known method to prepare pyrazoles is from the reaction between aliphatic diazo compounds and acetylene derivatives. The most commonly used diazo compounds are diazomethane and ethyl diazoacetate. Below is an example of diazomethane reacting with acetylene to generate 1H-pyrazole (3).¹² Another

similar method is diazo compounds reacting with olefins to generate pyrazolines

(4).¹³



Another popular method to prepare pyrazolines is the addition of hydrazines to α,β -unsaturated carbonyl compounds. This method was discovered by Fisher *et al.* in 1887. Since then, a wide variety of pyrazolines have been synthesized by this method. For example, a series of pyrazolines was prepared by reacting hydrazines or its derivatives with α,β -unsaturated carbonyl compounds in the present of microwave irradiation (5).¹⁴ There are many other known methods for the preparation of pyrazoles. For example, pyrazoles can be prepared from 1,2,3-tricarbonyl compounds with hydrazine and its derivatives;¹⁵ Also, from α -halocarbonyl compounds with mono- and dithiocarbohydrazides.¹⁶



Pyrazole compounds have major applications in the pharmaceutical field. Unsubstituted pyrazole shows no antimicrobial activity, but 3-, 4- and/or 5-alkyl or phenylpyrazoles inhibit *Aspergillus niger* (Figure 2)¹⁷ and *Staphylococcus aureus*.¹⁸

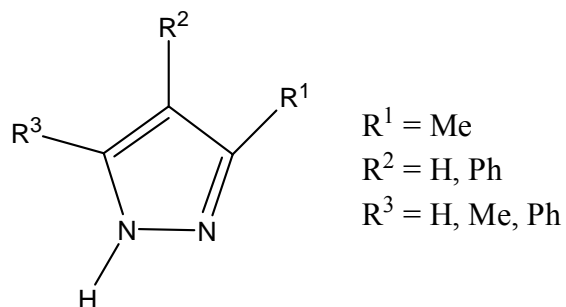


Figure 2. Substituted pyrazoles with antimicrobial activity.

Pyrazoles can not only be prepared in the lab, they also occur in nature. 3-n-Nonylpyrazole was the first natural pyrazole derivative to be isolated from

Houttuynia cordata, a plant of the “piperaceae” family from tropical Asia, and was observed to have antimicrobial activity.¹⁹ A pyrazolic amino acid *levo*- β -(1-pyrazolyl)alanine was isolated from water melon seeds,²⁰ which also has antibiotic activity (Figure 3).

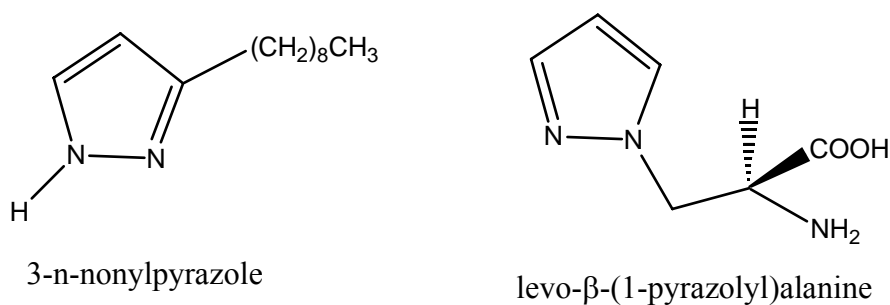


Figure 3. Naturally occurring pyrazoles with antibiotic activity.

A current commercial drug known as CelebrexTM is a pyrazole compound. Celebrex is a drug that is used to treat arthritis, pain, and menstrual cramps (Figure 4).

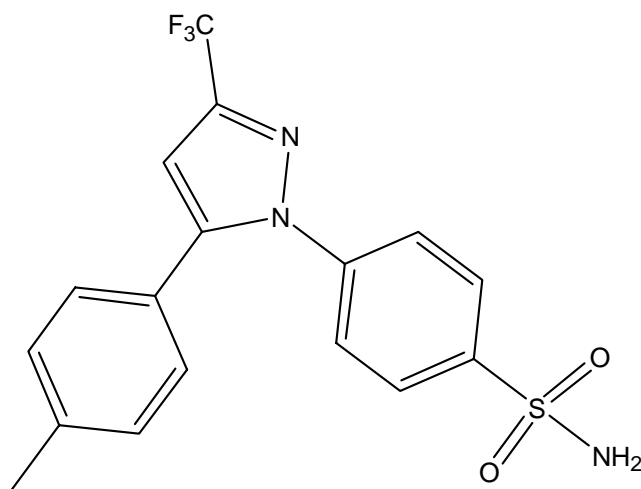


Figure 4. Structure of the commercial drug known as CelebrexTM.

2-(1-Pyrazol-1-yl)pyrimidines are a type of pyrazole that show promises as microbicides due to their activity against *Piricularia oryzae*, *Pellicularia sasakii*, and *Helminthosporium oryzae* on rice (Figure 5).²¹

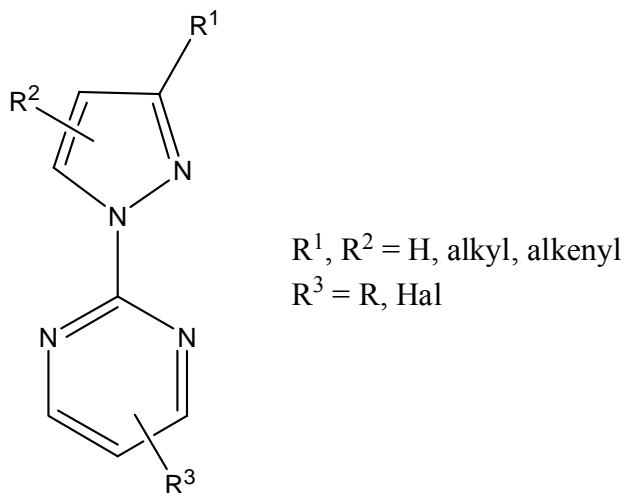
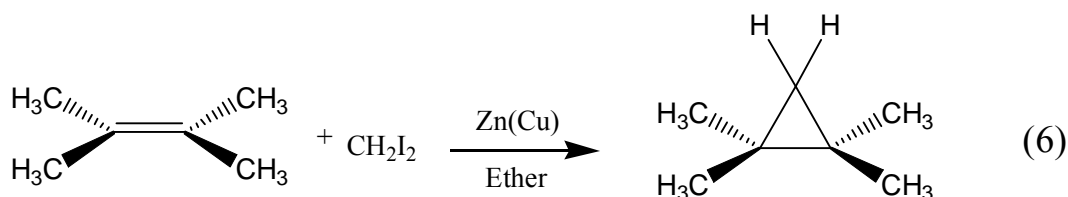


Figure 5. 2-(1-Pyrazol-1-yl)pyrimidines

1. 2 Cyclopropanes

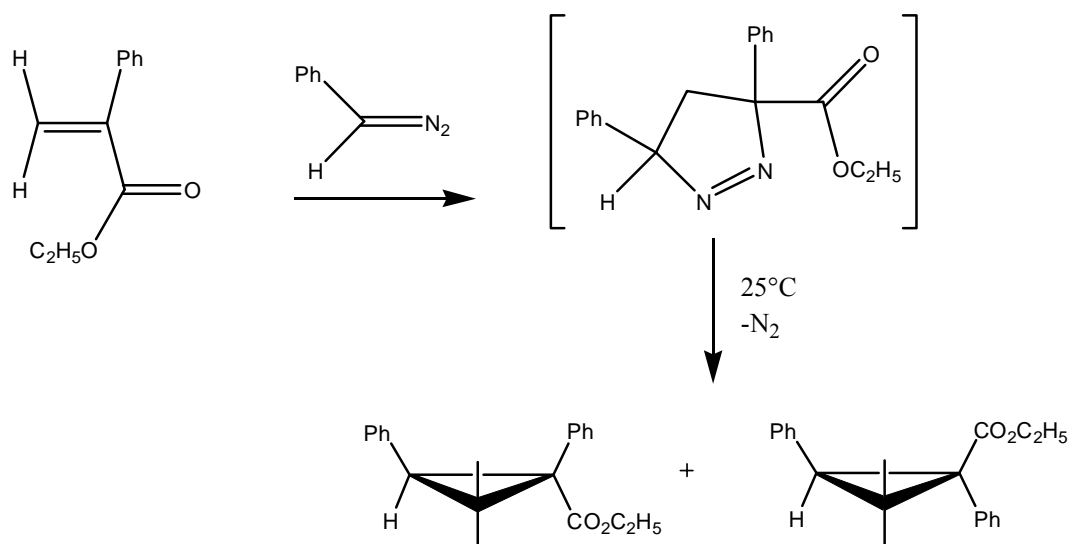
Cyclopropanes are unique among carbocycles in both their properties and reactions.²² Some of the reactive cyclopropyl radicals generated from decomposition of cyclopropanes are useful due to their unique bonding, which affords a tool to study the mechanism of a variety of reactions.²³ The synthesis of cyclopropanes has been accomplished over the years by a variety of methods.^{24,}
26, 31

The two common methods to cyclopropanes are carbene and carbenoid additions to olefins. A classic example of this type of reaction is the Simmons-Smith reaction (6). A carbenoid is generated when diiodomethane is treated with specially prepared zinc-copper alloy, which then react with alkenes to form cyclopropanes.²⁴



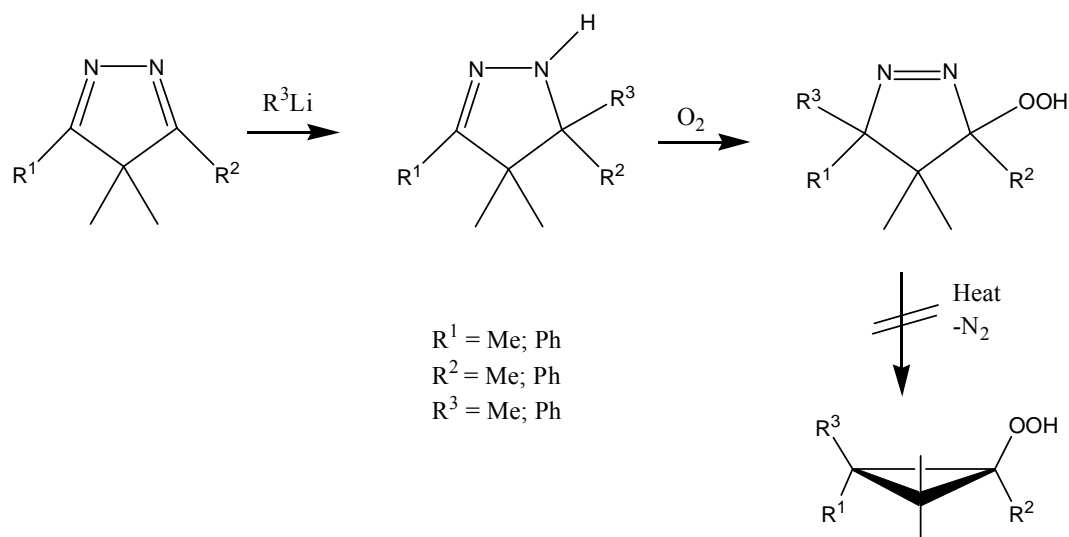
One of the simplest ways to generate free carbene species is to treat chloroform with a strong base such as potassium hydroxide. The generation of carbenes from diazo compound has also been widely used.³⁷ However, these types of reaction are usually limited to tetra-aryl/alkyl-or less substituted cyclopropanes because disubstituted carbene or carbenoids typically do not add to tetra-substituted olefins.²⁵

Another important type of cyclopropane formation reaction is 1,3-dipolar diazo compound additions to olefins to yield pyrazolines with subsequent thermal or photochemical extrusion of nitrogen.²⁶ An example of this type of reaction is on Scheme 1.²⁷ Again, this method is generally limited to the preparation of tetra- or less substituted cyclopropanes.²⁸ The synthesis of penta-alkyl/alkoxy or acetoxy cyclopropanes has been reported in a few special cases.²⁹



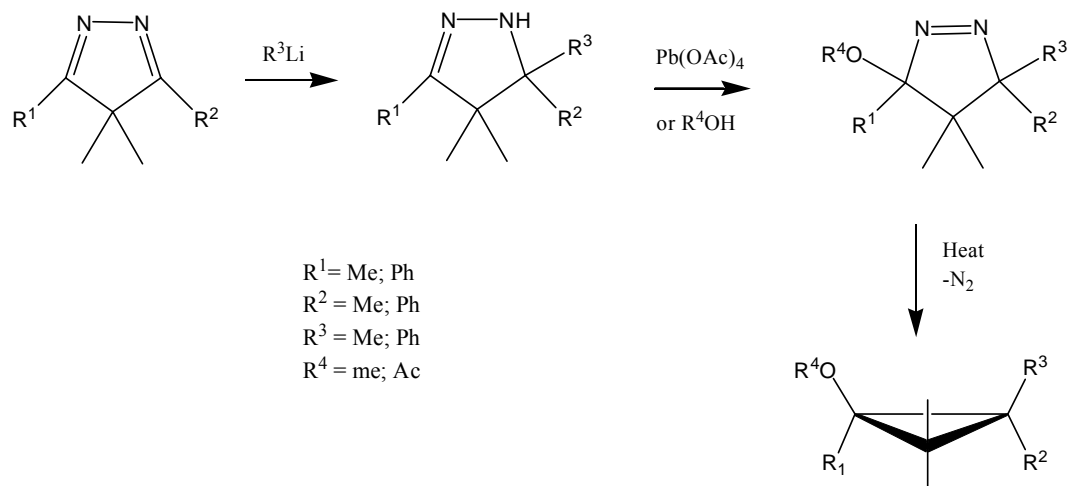
Scheme 1. Example of 1,3-dipolar cyclic addition followed by extrusion of nitrogen.²⁷

Several years ago, Baumstark *et al.* reported the development of a new general method to hexasubstituted-4,5-dihydro-3H-pyrazoles. This method involves the addition of organolithium reagents to 4,4-dimethyl-3,5-disubstituted-4H-pyrazoles followed by an autoxidation process to produce α -azo hydroperoxides (Scheme 2).¹¹ However, thermal decomposition of these hexasubstituted α -azo hydroperoxide pyrazolines did not produce cyclopropanes.



Scheme 2. General method to hexasubstituted 3H-pyrazoles (Baumstark *et al.*, 1990).

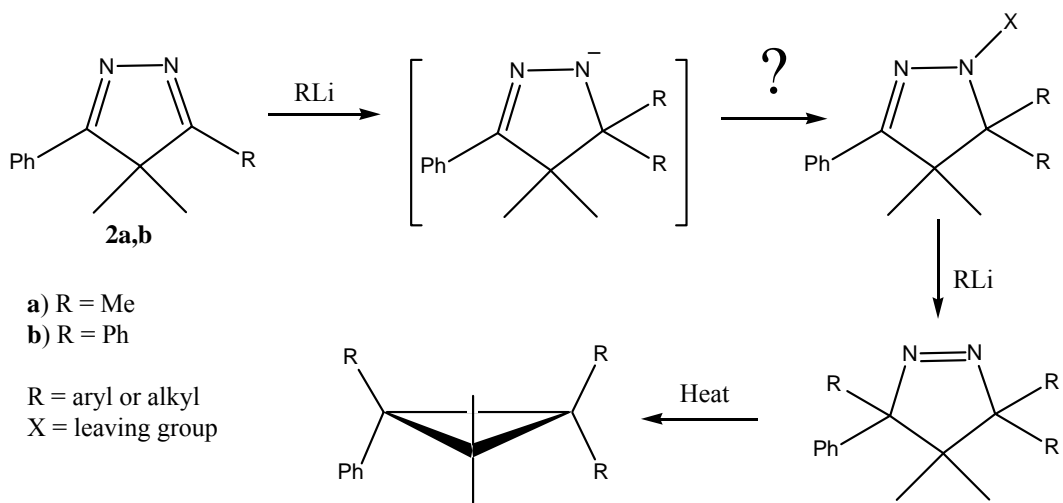
Kennedy *et al.* used the same approach to synthesize a series of 5-alkoxy and 5-acetoxy-3,5,5-trisubstituted-4,5-dihydro-3H-pyrazoles, thermolysis of which produced the corresponding 1-alkoxy and 1-acetoxy-1,2,2,3,3-penta-aryl/alkylsubstituted cyclopropanes (Scheme 3).³¹ This method suggested a general route to highly substituted cyclopropanes (Scheme 3).



Scheme 3. A general method to highly substituted cyclopropanes (Kennedy et al., 1991).

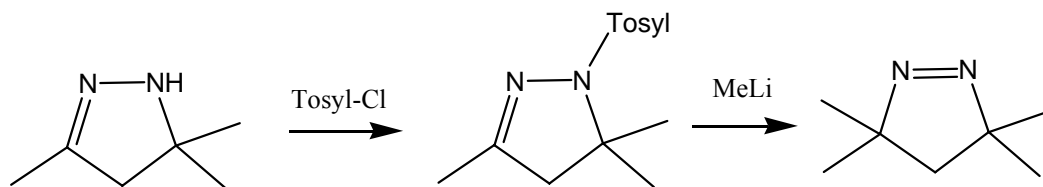
1. 3 Statement of Problem

Although, there have been reports on the synthesis of hexa-aryl/alkylsubstituted- cyclopropanes, a general method to these compounds is not readily available. Recently, our laboratory have developed a method to fully substituted-cyclopropanes by thermal decomposition of pyrazolines.³¹ The goal of this research is to develop a new general methodology to hexa-aryl/alkylsubstituted-cyclopropanes by capitalizing the recently published method that involves the decomposition of pyrazolines. Our approach to the synthesis of hexa-aryl/alkylsubstituted-cyclopropanes begins with the azines **2a,b** (Scheme 4). Alkyl lithium reagents have been shown to alkylate the 4H-pyrazoles **2a,b** at the carbon-nitrogen double bond to generate a nitrogen anion intermediate.¹¹ If this nitrogen anion could be trapped with a good leaving group, then addition of a strong alkyl nucleophile should attack the carbon-nitrogen double bond in S_N2 type to displace the leaving group and generate hexa-aryl/alkylsubstituted-pyrazolines. Accordingly, thermolysis of this type of pyrazolines should readily result in the formation of hexa-aryl/alkylsubstituted-cyclopropanes.



Scheme 4: Our approach to hexa-aryl/alkylsubstituted-cyclopropanes

One literature reference was found that shows similar chemistry to our approach. Engle *et al.* has an example showing that 3,5,5-trimethyl-4,5-dihydro-1H-pyrazoles could be tosylated at the nitrogen position by reacting it with tosyl-chloride (Scheme 5). Then, addition of methyl lithium at the carbon-nitrogen double bond with resulting detosylation generated 3,3,5,5-tetramethyl-4H-pyrazole (Scheme 5).³² This example indicated a tosyl group would be a potential candidate to for a good leaving group, and tosyl-chloride could be used as nitrogen tosylation reagent.

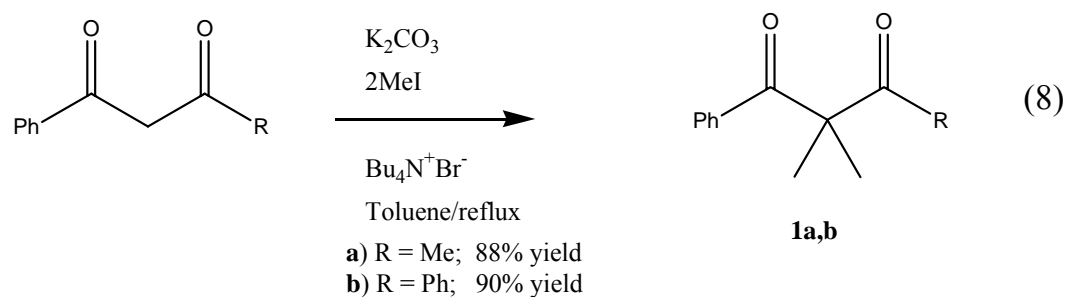


Scheme 5. Nitrogen tosylation by addition of tosyl-chloride.

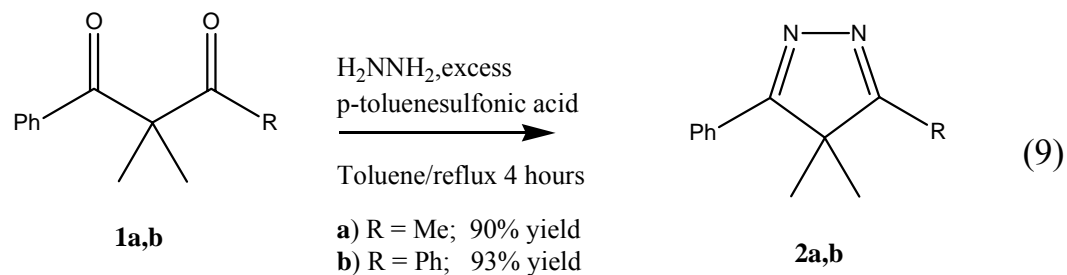
Chapter 2

2.1 Results

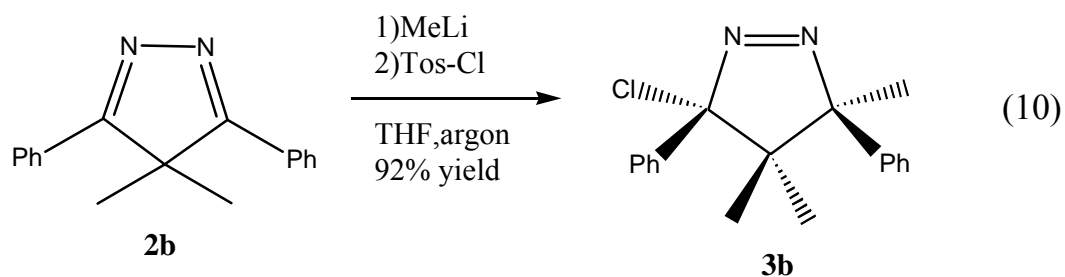
The synthesis of hexa-alkyl/arylsubstituted-cyclopropanes began by dimethylating 1,3-diketones to prepare 2,2-dimethyl-1,3-diketones **1a** and **1b** (8). The commercially available diketones were dialkylated in a toluene solution and under basic condition in the present of a phase transfer catalyst.³³



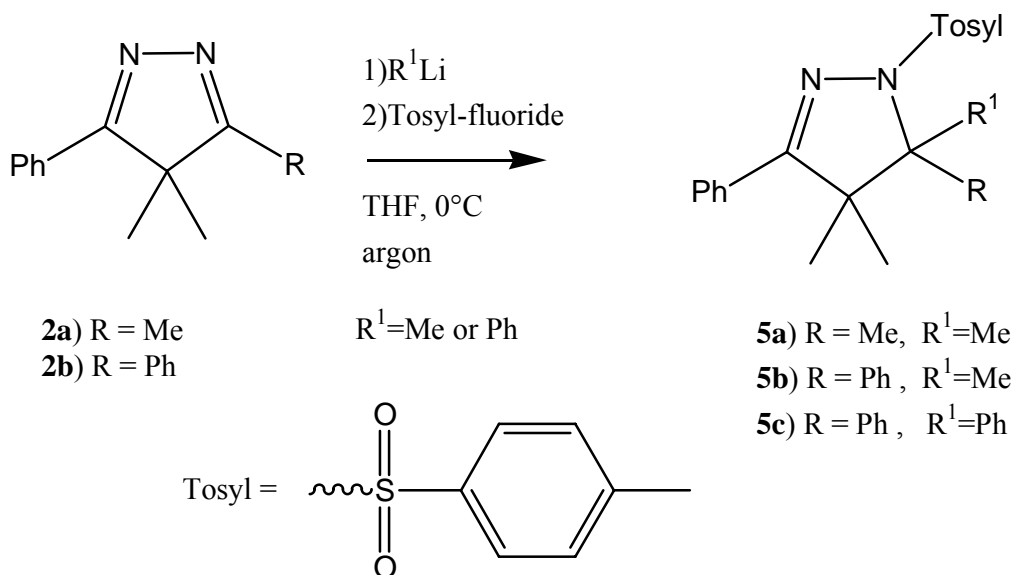
The next step was the preparation of the 4H-pyrazoles **2a** and **2b** from **1a** and **1b**. This condensation reaction took place by addition of hydrazine to **1a** and **1b** in the presence of a catalytic amount of p-toluenesulfonic acid under standard reflux condition in toluene, equipped with a Dean-Stark trap (9).¹¹



As the literature suggested, alkyllithium reagents will alkylate **2a,b** at the carbon-nitrogen double bond to generate the nitrogen anion. Tosyl-chloride was used to trap the nitrogen anion with a tosyl-group, but the reaction did not yield the expected nitrogen tosylated product. The major product generated from the addition of methyl lithium followed by tosyl-chloride to **2b** is 3-chloro-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole **3b** (10).³⁴

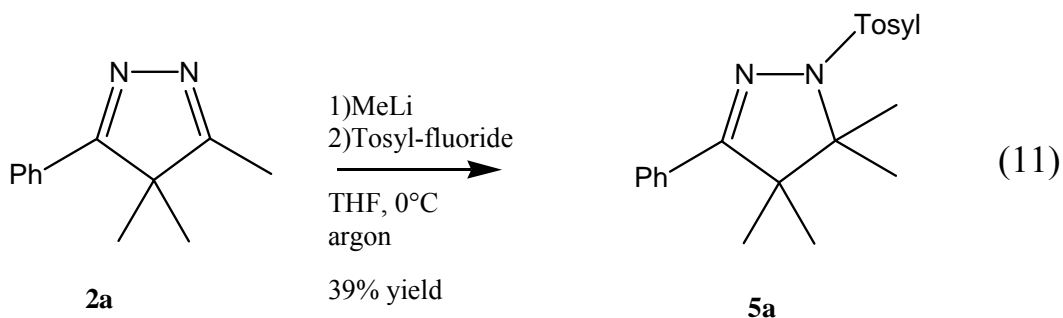


However, addition of alkyllithium followed by tosyl-fluoride to **2a** and **2b** alkylated the carbon-nitrogen double bond and trapped the nitrogen anion with a tosyl group (Scheme 6).

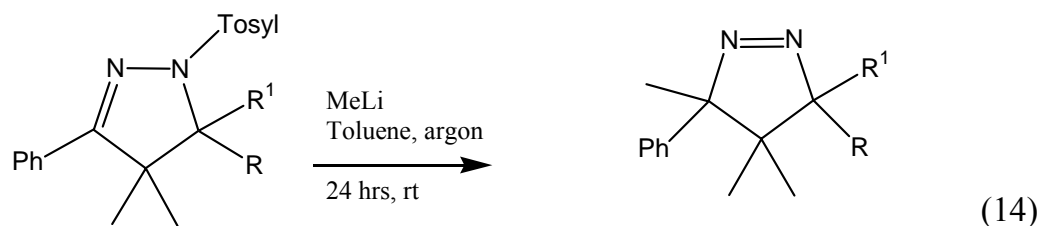


Scheme 6. Addition of alkyl lithium and tosyl-fluoride to the cyclic azines **2a** and **2b**.

The synthesis of **5a** was accomplished in 39% yield by addition of methyllithium and tosyl-fluoride to **2a** (11). The other side products have not been purified or characterized.



The synthesis of **5b** was accomplished in 91% yield by additions of methyllithium and tosyl-fluoride to **2b** (12). This is a high yield reaction and the product can be easily purified by recrystallization. Compound **5b** was recently reported as a by-product (8% yield).³⁰



5a) R = Me, R¹=Me

5b) R = Ph, R¹=Me

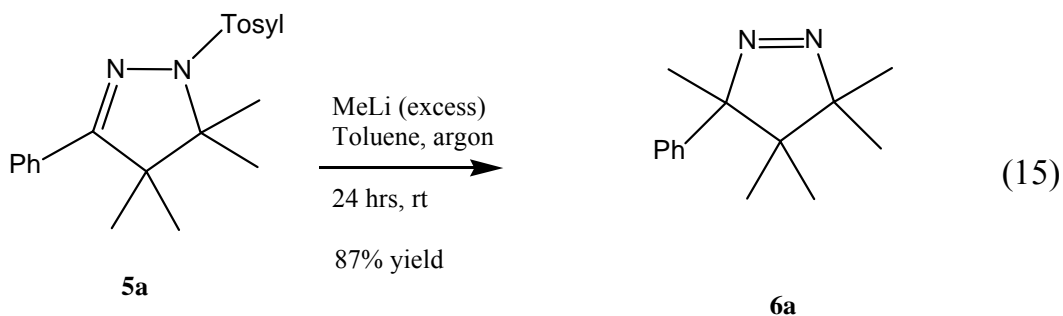
5c) R = Ph, R¹=Ph

6a) R = Me, R¹=Me

6b) R = Ph, R¹=Me

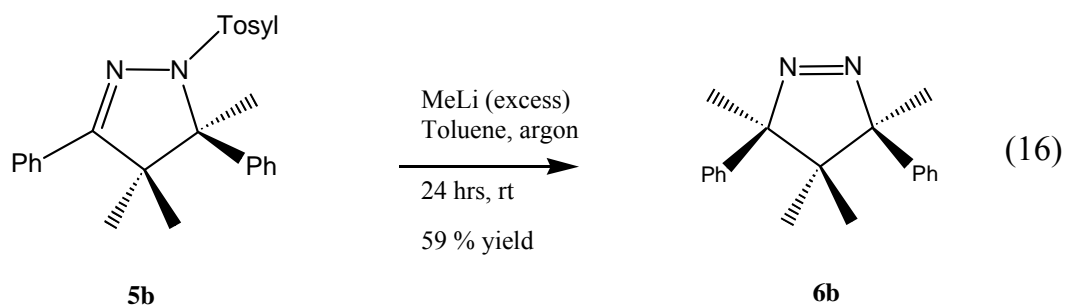
6c) R = Ph, R¹=Ph

The synthesis of **6a** was accomplished by addition of methyllithium to **5a** (15). This reaction gave 87% isolated yield and only one product was generated. Based on GC/MS and ¹HNMR of the crude product, the other 13% is unreacted material.

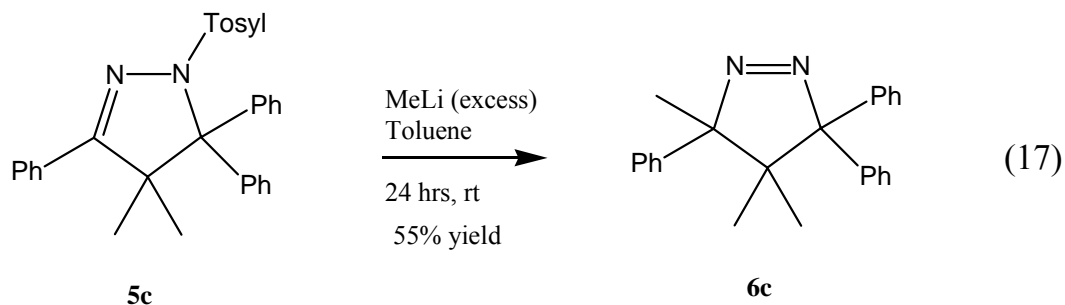


The synthesis of **6b** was accomplished by addition of methyllithium to **5b** (16). This reaction is highly regiospecific. The methyl group only added to the opposite side of the 5-phenyl group, which resulted in the 3,5-diphenyl groups being in the cis position. This reaction only produced **6b** in 59% isolated yield,

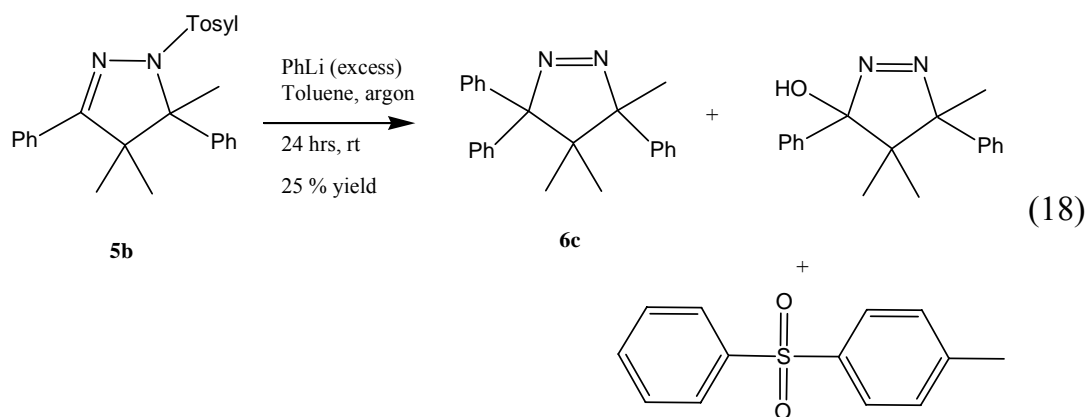
but based on GC/MS and ^1H NMR of the crude product, the other 41% is unreacted starting material.



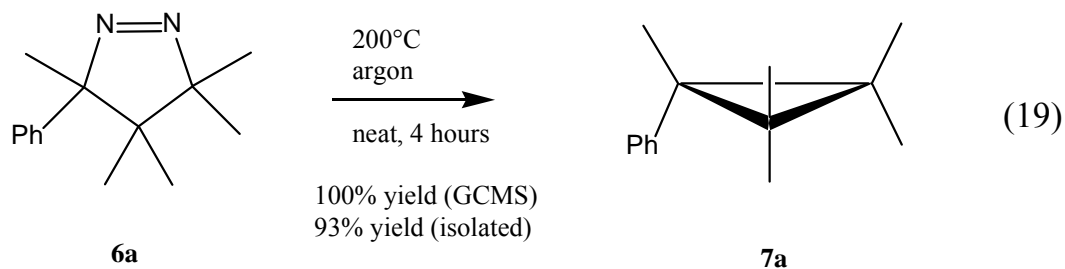
The synthesis of **6c** was accomplished by addition of methyllithium to **5c** (17). This reaction gave 55% isolated yield of **6c**. Again, the other 45% is unreacted starting material based on GC/MS and ^1H NMR of the crude product.



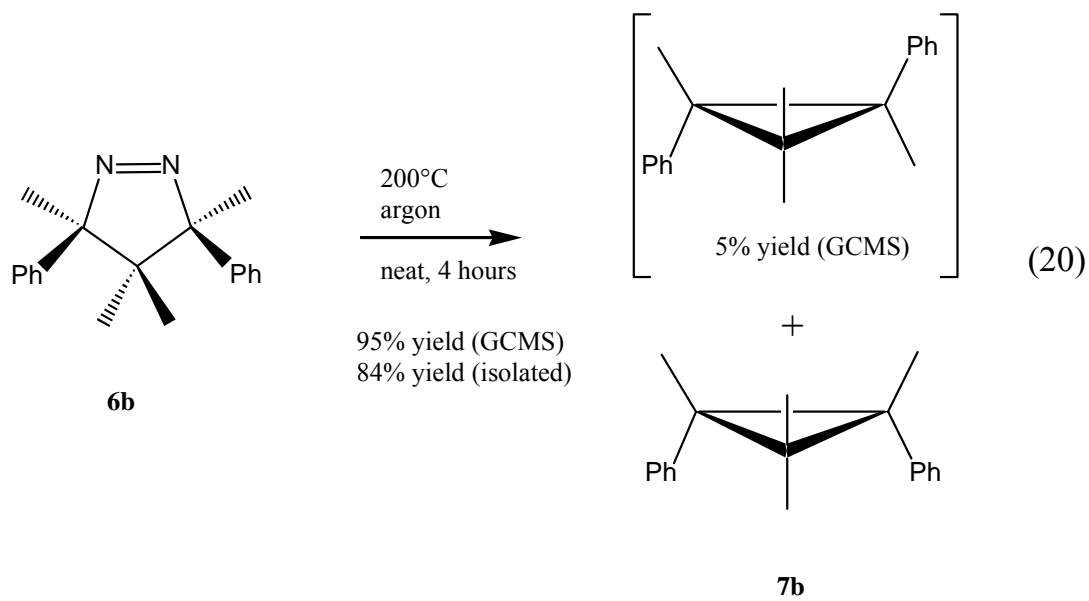
A different method for the synthesis of **6c** was to add phenyllithium to **5b** (18). However, this reaction produced **6c** in low yield (25%) because the phenyl not only attacked the carbon-double bond, but it also attacked the sulfur atom of the tosyl group to yielded phenyl-p-tosylsulfone (18).



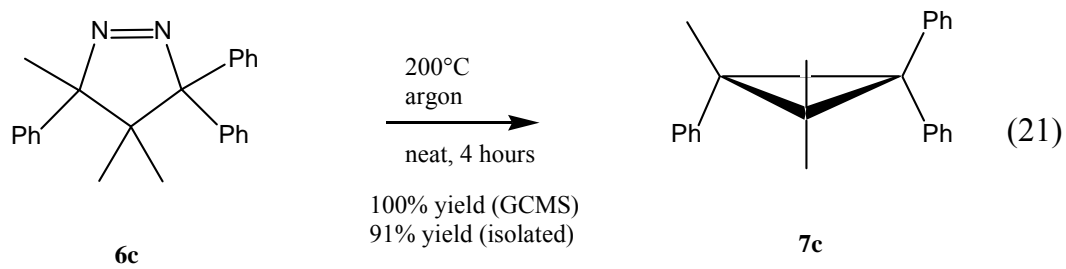
The synthesis of hexa-aryl/alkylsubstituted-cyclopropanes (**7a-7c**) was accomplished by neat thermolysis of hexa-aryl/arylsubstituted-3H-pyrazoles (**6a-6c**) (Scheme7). Thermolysis of **6a** gave **7a** in 93% isolated yield (19).



Thermolysis of **6b** yielded 5% of the *trans* and 95% of the *cis* isomers of **7b** based on GC/MS (20). However, only 84% of the *cis* product was isolated. An X-ray structure for **7b** was obtained by Kenneth Hardcastle at Emory University to confirm the identity of this isomer (Figure 6).



Thermolysis of **6c** produced **7c** in 92% isolated yield (21).



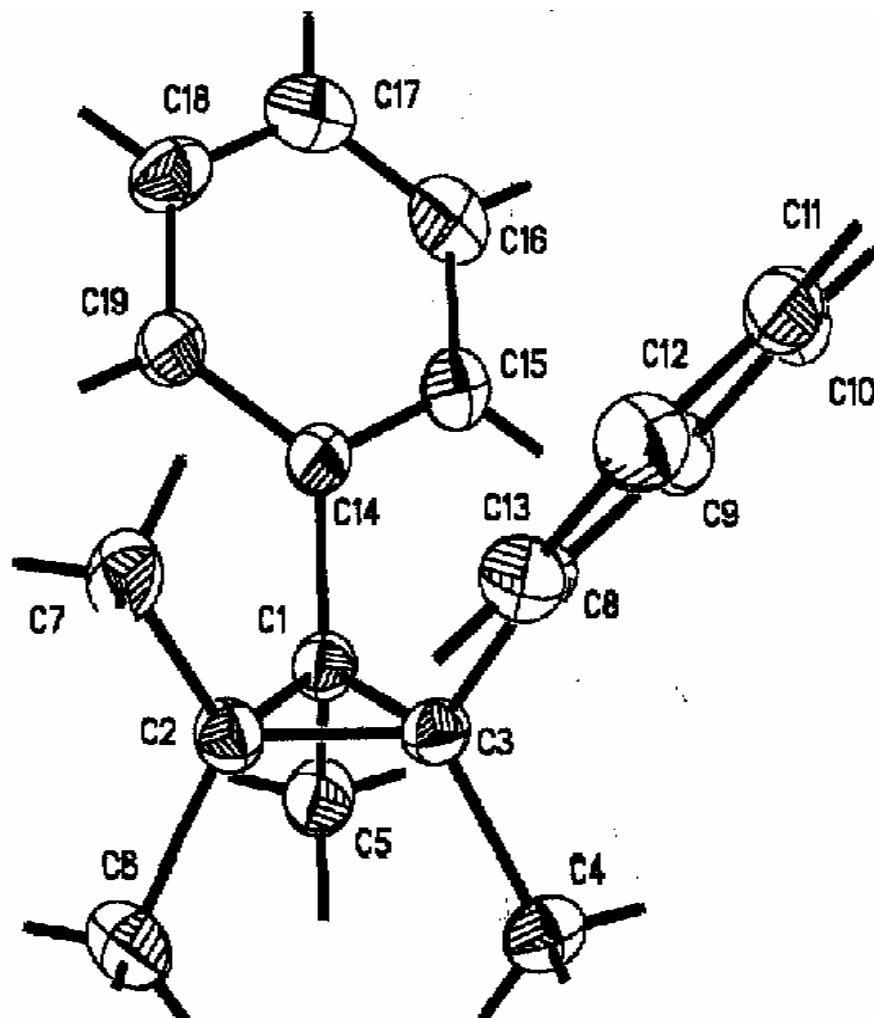
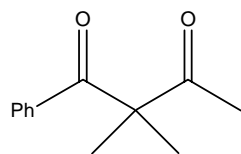
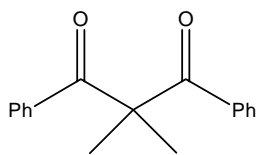


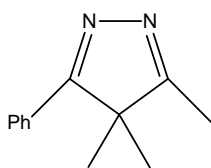
Figure 6. X-ray structure for 7b.



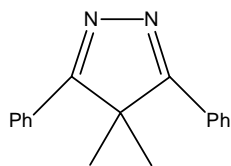
1a mp=(82-83)°C



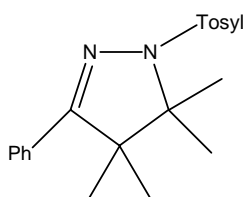
1b mp=(98-99)°C



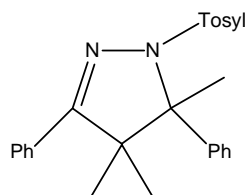
2a mp=(95-96)°C



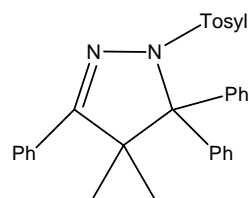
2b mp=(126-127)°C



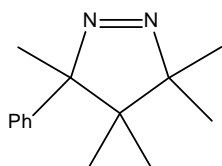
5a mp=(113-114)°C



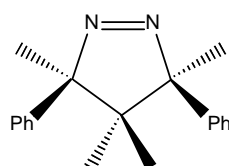
5b mp=(169-170)°C



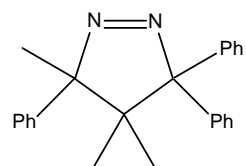
5c mp=(240-242)°C



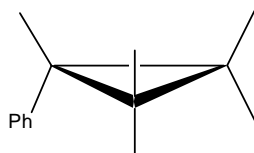
6a (clear liquid)



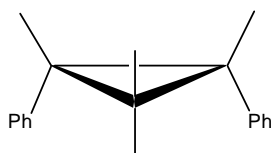
6b mp=(144-145)°C



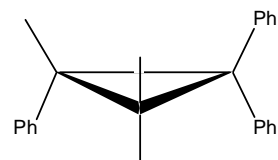
6c mp=(117-118)°C



7a (clear liquid)



7b mp=(79-81)°C



7c (clear liquid)

Scheme 7. A list of synthesized compounds and their melting points.

2. 2 Discussion

The present approach to hexa-aryl/alkylsubstituted-cyclopropanes provide a new general method for the synthesis of a variety of hexa-aryl/alkylsubstituted-3H-pyrazoles, thermolysis of which produced a series of hexa-aryl/alkylsubstituted-cyclopropanes. There have been a large number of publications on the mechanism of cyclopropanes formation by decomposition of pyrazoles. The results support a simultaneous carbon-nitrogen bond breakage in systems that have radical stabilizing substituents at one and five position. However, when substituents are non-radical stabilizing, a range of mechanistic behavior occurred, from simultaneous carbon-nitrogen breakage to two steps non-synchronous breakage (Figure 7).³⁶ The decomposition mechanism for hexa-aryl/alkyl substituted-3H-pyrazole systems has never been published. This research provides necessary compounds to get better insight for the mechanism of cyclopropane formation.

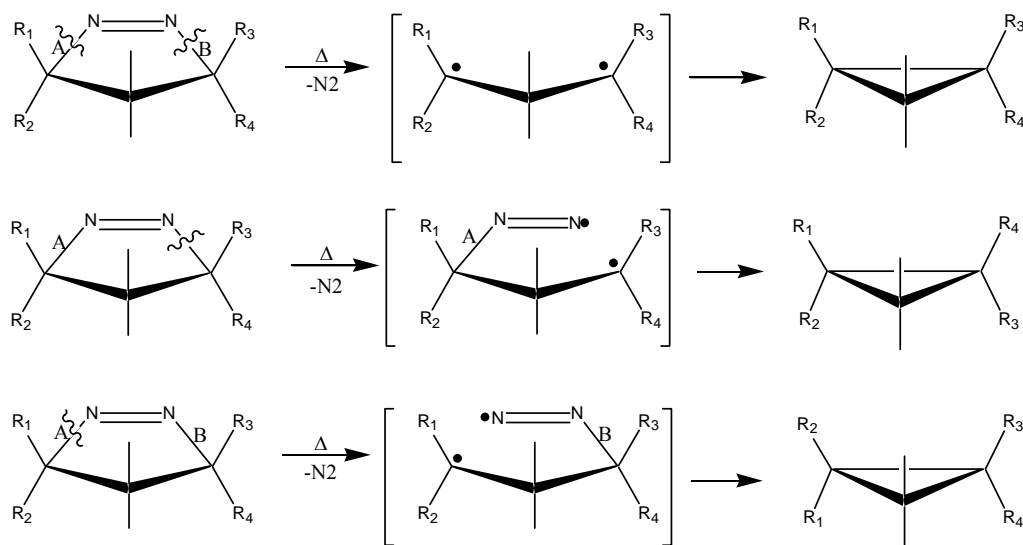
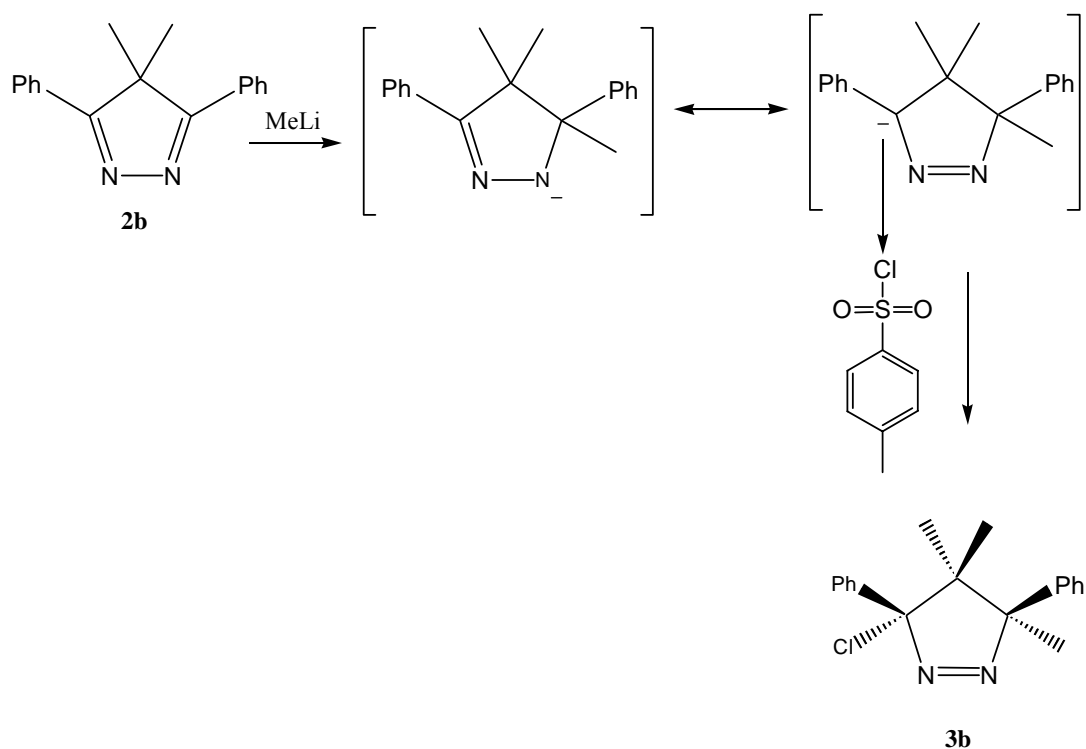


Figure 7. Possible pathways of bond breakage in 3H-pyrazoles when the substituents are non-halogenated.

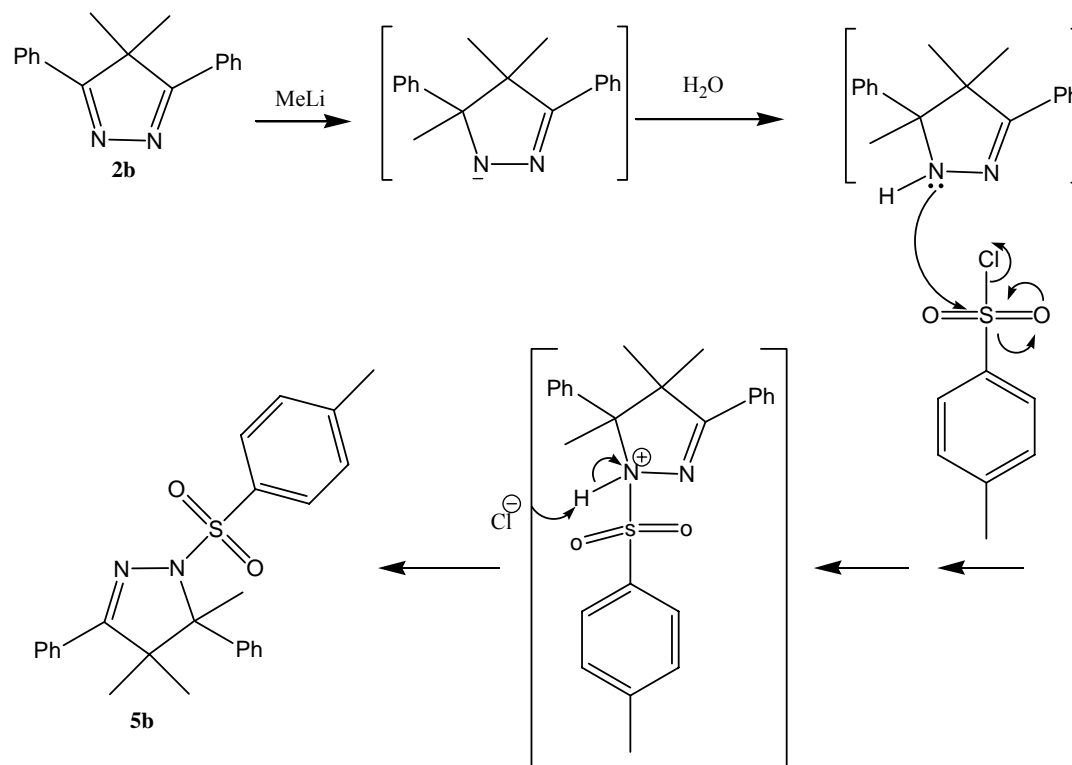
One of the most difficult tasks in this project was trapping the nitrogen anion with a leaving group. It's shown by Engle et al. that the tosyl could be a good leaving group, and it could be attached to the nitrogen by using tosyl-chloride. However, the attempts to trap the nitrogen anion with tosyl-chloride was unsuccessful because the major product for this reaction is 3-chloro-4,4,5-trimethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole **3b**.³⁴ It is thought that the nitrogen anion resonance to a tertiary anion, which attacked the chlorine in an S_N2 type reaction to form **3b** (Scheme 8).



Scheme 8: Nitrogen anion reacted with Tosyl-chloride

The desired nitrogen tosylated compound **5b** was able to isolated from this reaction as a minor product (8% yield).³⁵ The formation of **5b** is suggested to occur by N-hydrated intermediate reacted with tosyl-chloride (Scheme 9).

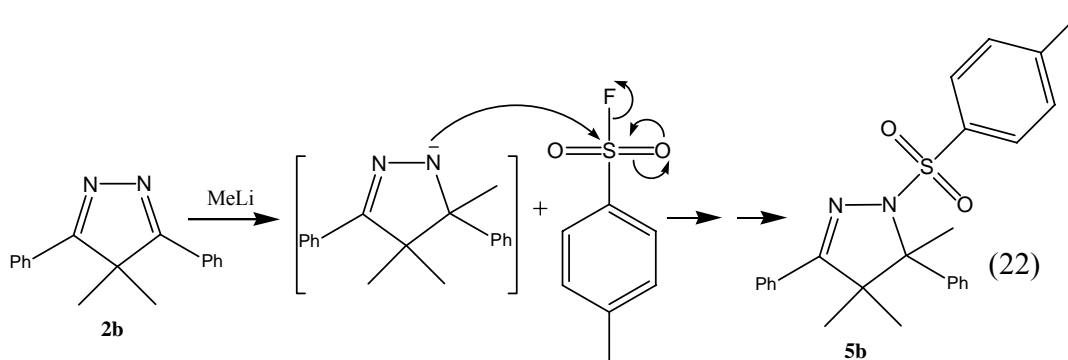
Although the reaction gave low yield to the desired N-tosyl product, however, it shows that the nitrogen anion could indeed be tosylated with tosyl-halide.



Scheme 9. Suggested mechanism for **5b** formation.

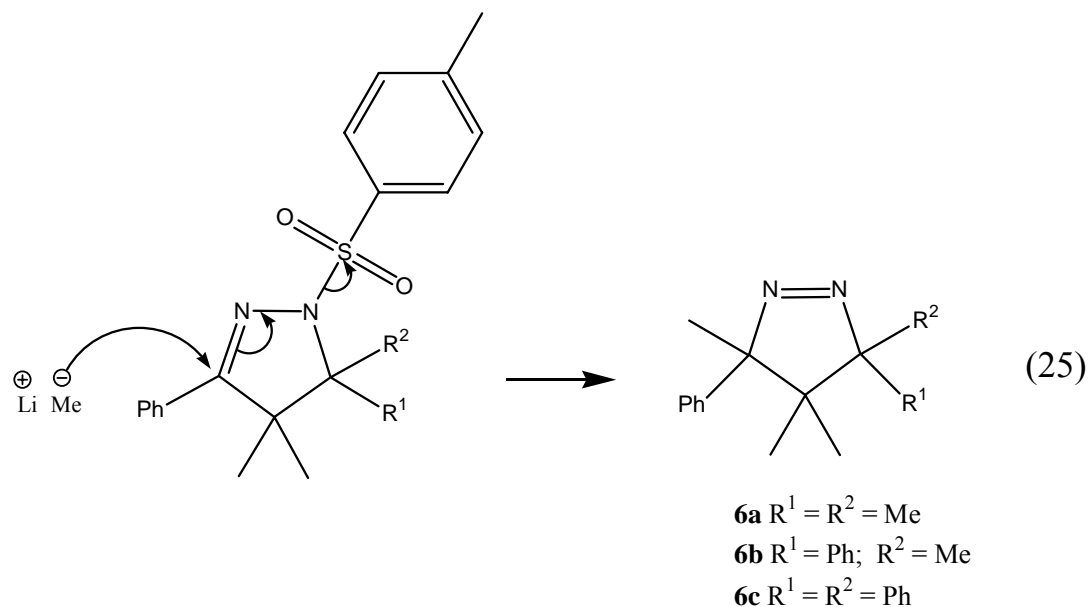
The idea for this reaction is to get the nitrogen anion to attack the sulfur and displace the chlorine anion. However, it is possible that the chlorine atom is too big and blocked the nitrogen anion from attacking the sulfur. Therefore, tosyl-fluoride was introduced because fluorine atom is much smaller than chlorine atom, which could increase the accessible site for the nitrogen anion to attack the sulfur. Also, fluorine has a higher electronegativity value than chlorine, which means the chance of a negatively charged anion to attack fluorine is smaller than chlorine. As a result, tosyl-fluoride gave high yield to the desired N-tosyl

compound **5a-c** (Scheme 10). This is the major step that leads to the synthesis of hexa-aryl/alkylsubstituted-cyclopropane.



Scheme 10: Nitrogen anion reacted with tosyl-fluoride.

Addition of methyllithium to **5a-c** yielded a series of hexasubstituted-4,5-dihydro-3H-pyrazole (**6a-c**). Although, the yield for these reactions are not as high (~50-60 %), but only the expected products were formed. The other portions are unreacted starting material, no other side products were observed in these reactions. These reactions were accomplished by addition of 4-fold excess of methyllithium reagent. Perhaps, better yields could be achieved by increases with an excess of methyllithium. A proposed mechanism for the synthesis of hexa-arylalkylsubstituted-4,5-3H-pyrazoles **6a-c** is shown below (25).



The synthesis of **6b** is a highly regioselective reaction. Only the *cis* isomer was generated from adding methyllithium to **5b** (Figure 8). The methyllithium attacks **5b** at the carbon-double bond with only respect to the same side of the 5-methyl group. This is reasonable since the size of the methyl group is smaller than the phenyl, which means more accessible and less steric hinderance. Therefore only the *cis* isomer was generated.

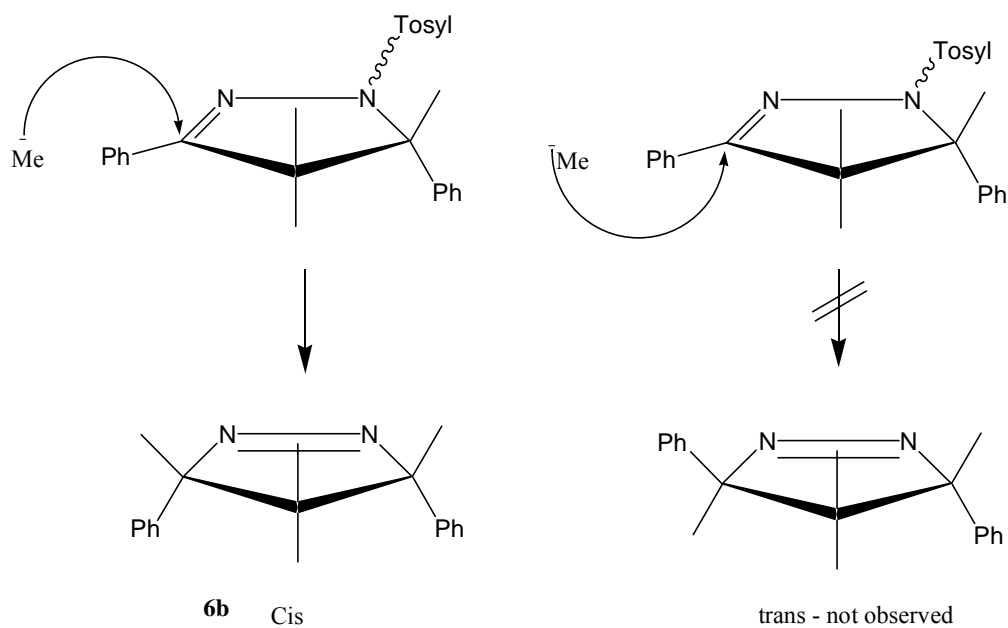


Figure 8. Stereochemistry of addition methyllithium to **5b**.

The ^1H NMR spectrum of **6b** has a very unique characteristic. The spectrum showed a signal for one of the 4,4-dimethyl groups to be -0.26 ppm, up-field from tetramethylsilane (TMS) (Figure 9). This signal was assigned to the methyl group that lies between the two-phenyl rings. The ring current of the phenyl groups shielded the methyl peak, which caused the chemical shift to be up-field from TMS.

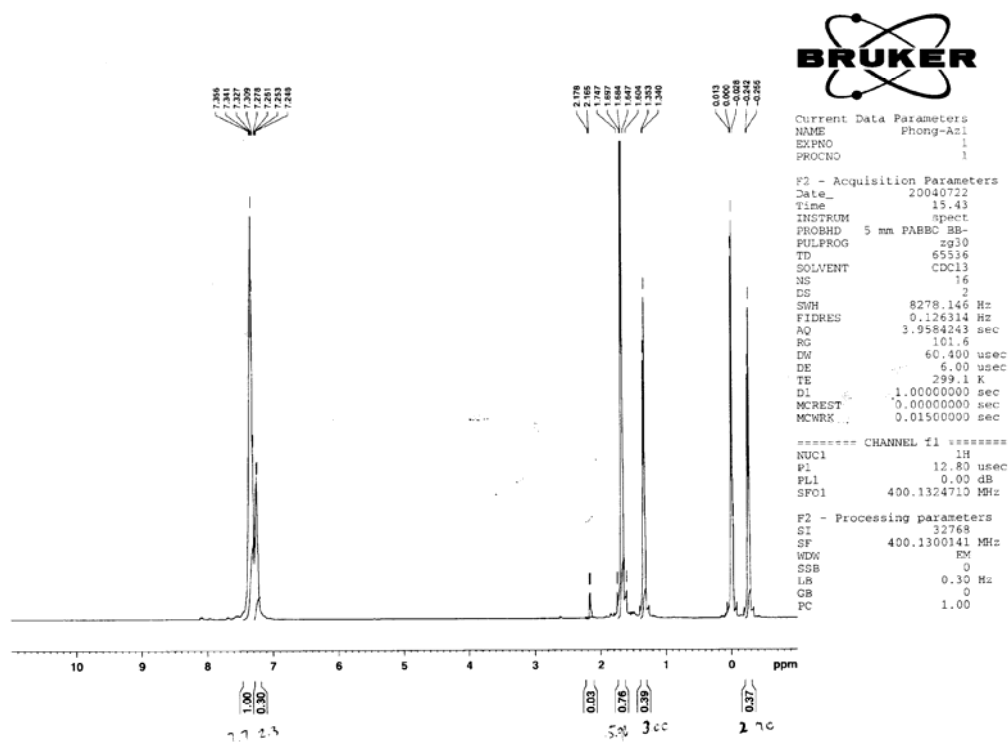
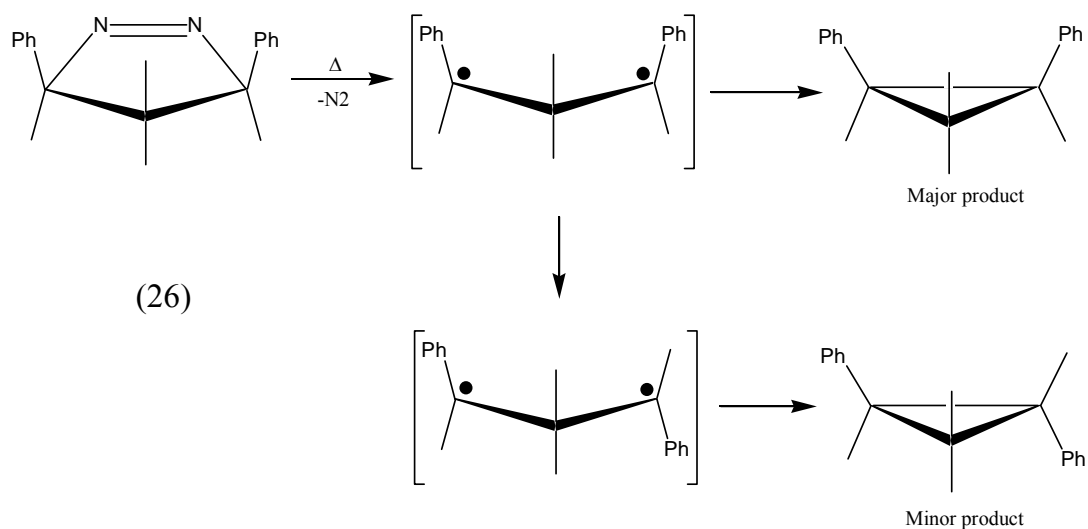


Figure 9. ^1H NMR spectrum of **6b**.

Phenyllithium behaved a little different from methylolithium when reacted with **5b**. The phenyl group not only attacked the carbon double bond, but it also attacked the sulfur on the tosyl group, which generated phenyl-p-tosyl sulfone and nitrogen anion intermediate. The nitrogen anion intermediate then oxidized into α -azoperoxides, and reduced to α -azohydroxides (Figure 10).

mechanism of simultaneously carbon-nitrogen bond breakages. The major product “*cis*” was generated by simultaneously breakage of the carbon-nitrogen bonds to form a 1,3-diradical intermediate, which undergoes intramolecular coupling to the product corresponding to retention of stereochemistry. The singlet 1,3-diradical intermediate undergoes a bond rotation then coupling to generated the minor product *trans* (26).



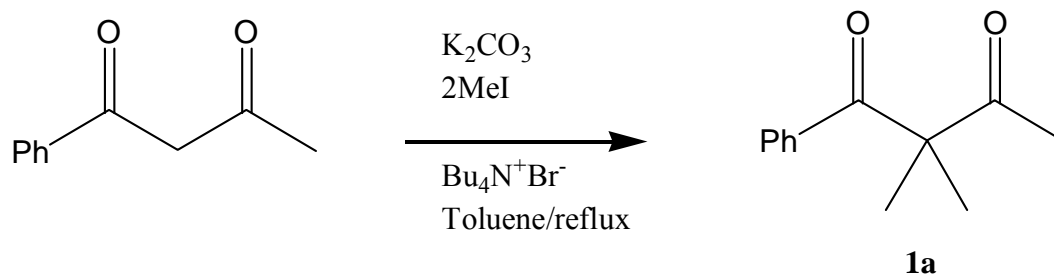
2. 3 Conclusion

We have developed a general method for the preparation of hexa-alkylaryl-4,5-3H-pyrazoles. The thermolysis of these pyrazoles proved to be a general method to hexa-aryl/alkylsubstituted-cyclopropanes.

Chapter 3

Experimental

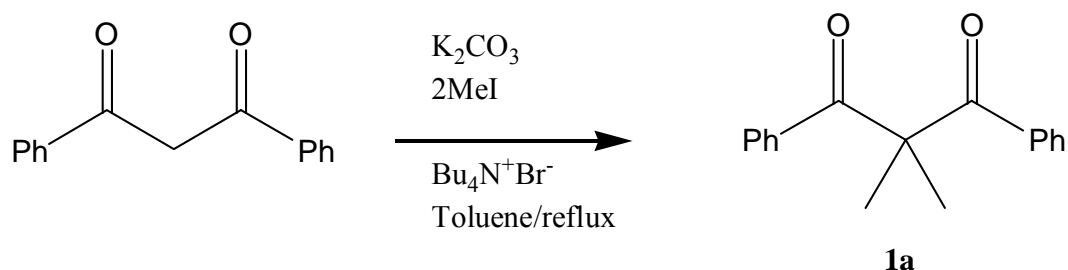
The following reagents were purchased from Sigma-Aldrich Company and used without further purification: methyllithium (1.6M) in diethyl ether, phenyl lithium (1.8M) in cyclohexane-ether, iodomethane (99%), p-toluenesulfonyl chloride (99%), p-toluenesulfonyl fluoride (98%), N-bromosuccinimide (99%), tertbutylammonium bromide, dibenzoylmethane (98%), 1-benzoylacetone (99%), potassium carbonate (99.7%), anhydrous hydrazine (98%), anhydrous magnesium sulfate (97%), ammonium chloride (99%). All solvents were commercially available. Anhydrous toluene, anhydrous ether, and methanol were purchased from Aldrich Company and used without further purification. Tetrahydrofuran (Aldrich) was distilled over sodium and benzophenone before use. Acetone, ethanol, and hexane were purchased from Fisher Scientific Company. All ^1H and ^{13}C NMR spectra were obtained from Varian Unity Plus 300 MHz instrument. Mass spectra were obtained from a Shimadzu GP-5000 Mass Spectrometer. Elemental analyses were performed at the Department of Chemistry at Georgia State University and at Atlantic Microlab, Atlanta, Georgia. Melting points were recorded in a calibrated Thomas Hoover Unimelt apparatus. Exact mass analyses were performed at Georgia Institute of Technology. X-ray crystallography was performed at Emory University.



Preparation of 2,2-dimethyl-1-phenyl-3-methyl-1,3-propanedione(1a)

Preparation of **1a** was accomplished by following the previous reported procedure.²⁹ Anhydrous toluene (250ml), 1-phenyl-1,3-butanedione (10 g, 0.06172 mol), anhydrous potassium carbonate (29.82 g, 0.2158 mol), and tertbutylammonium bromide (0.3970g, 1.233 mmol) were mixed in a 500ml three neck round bottom flask, equipped with a Dean-Stark apparatus under argon atmosphere. The mixture was stirred vigorously and heated under reflux for 2 hours. The mixture was cooled down to room temperature and methyl iodide (10ml, 0.1541mol) was added over 1 hour period. The mixture was stirred at room temperature for three additional hours. A second portion of anhydrous potassium carbonate (29.82 g, 0.2158 mol) and tetrabutylammonium bromide (0.3970 g, 1.233 mmol) were added, and the mixture was heated under reflux overnight (12 h). The mixture was cooled down to room temperature, and a second portion of methyl iodide (10.0ml, 0.1541 mol) was added over a period of 1 hour. The mixture was stirred at room temperature for three hours and heated under reflux for four additional hours. After cooling to room temperature, the inorganic salts were removed by vacuum filtration and washed with diethyl ether. The filtrates were washed with deionized water (3x50 ml) and dried over

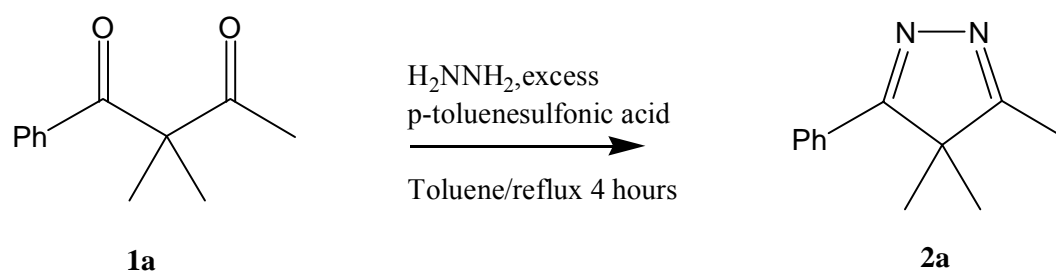
anhydrous magnesium sulfate. The solvents were removed under reduce pressure using a rotary evaporator. The crude oily residue was recrystallized from hexane to give the pure product with an isolated yield of 88% (10.3 g, 0.0541 mol) mp = 82-83°C (lit mp = 83°C)²⁹.



2,2-dimethyl-1,3-diphenyl-1,3-propanedione(1b)

Preparation of **1b** was accomplished by following the previous reported procedure.²⁹ Anhydrous toluene (250ml), dibenzoylmethane (10.0 g, 0.0446 mol), anhydrous potassium carbonate (29.82 g, 0.2158 mol), and tertbutylammonium bromide (0.3970g, 0.001233 mol) were mixed in a 500ml three neck round bottom flask, equipped with a Dean-Stark apparatus under argon atmosphere. The solution mixture was stirred vigorously and heated under reflux for 2 hours. The mixture was cooled down to room temperature and methyl iodide (10ml, 0.1541 mol) was added over 1 hour period. The mixture was stirred at room temperature for three additional hours. A second portion of anhydrous potassium carbonate (29.82 g, 0.2158 mol) and tetrabutylammonium bromide (0.3970 g, 0.001233 mol) were added, and the mixture was heated under reflux overnight (12 h). The mixture was cooled down to room temperature, and a second portion of methyl iodide (10.0ml, 0.1541 mol) was added over a period of 1 hour. The mixture was stirred at room temperature for

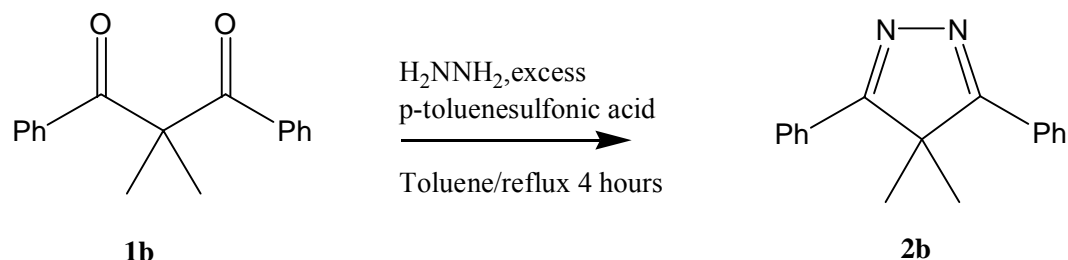
three hours and heated under reflux for four additional hours. After cooling to room temperature, the inorganic salts were removed by vacuum filtration and washed with diethyl ether. The filtrates were washed with deionized water (3x100 ml) and dried over anhydrous magnesium sulfate. The solvents were removed under reduce pressure using a rotary evaporator. The crude solid residue was recrystallized from ethanol to give the pure product with an isolated yield of 90% (10.1 g, 0.0396 mol), mp = 95-96°C (lit mp = 95-96°C)²⁹.



Preparation of 3,4,4-trimethyl-5-phenyl-4H-pyrazole (**2a**)

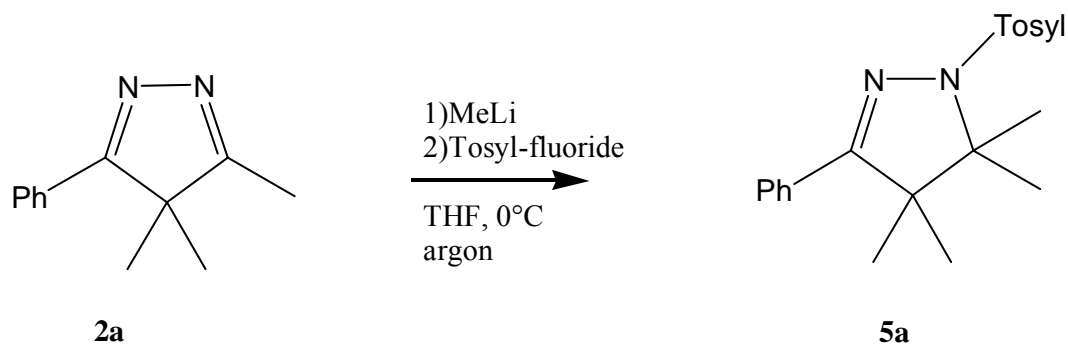
Preparation of **2a** was accomplished by following the previous reported procedure.⁷ Toluene (250ml), 2,2-dimethyl-1-phenyl-3-methyl-1,3-propanedione (**1a**) (9.0 g, 0.0473 mol) and P-toluenesulfonic acid (0.30 g) were mixed in a 500 ml three neck round bottom flask, equipped with a Dean-Stark and a condenser under argon atmosphere. Then 8ml (0.095 mol) of hydrazine was added with a glass syringe. The solution was heated under reflux for 5 hours. The solution was cooled down to room temperature and added the second batch of hydrazine (4ml, 0.0475 mol). The solution was heated again for 4 hours. After cooling to room temperature, the contents were removed from flask and washed with 5% NaHCO_3 solution (100ml) and dionized water (2x100ml). The solvent was dried over anhydrous magnesium sulfate and removed under reduced

pressure. The crude crystals were purified by recrystallized from hexane to give pure product with an isolated yield of 90% (8.2 g, 0.04402 mol), mp = 95-96°C (lit mp = 95-99°C)⁷.



Preparation of 4,4-dimethyl-3,5-diphenyl-4H-pyrazole (**2b**)

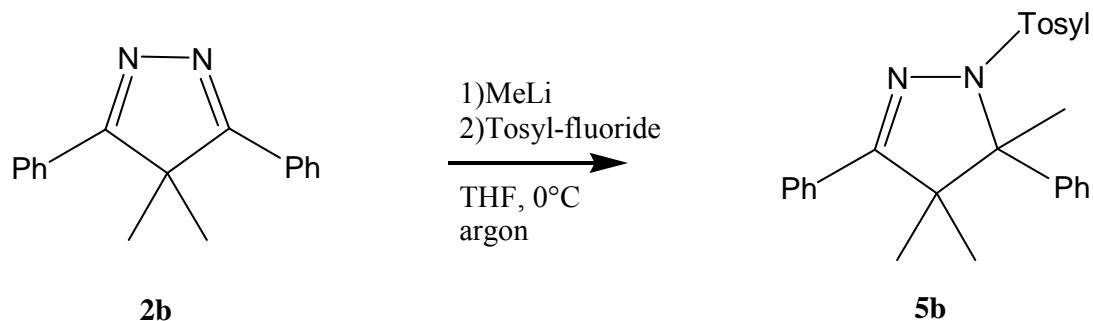
Preparation of **2b** was accomplished by following the previous reported procedure.⁷ Toluene (150ml), 2,2-dimethyl-1,3-diphenyl-1,3-propanedione (**1b**) (6.0 g, 0.02378 mol) and P-toluenesulfonic acid (0.30 g) were mixed in a 250 ml three neck round bottom flask, equipped with a Dean-stark and a condenser under argon atmosphere. Then hydrazine (4ml, 0.0475mol) was added with a glass syringe. The solution was heated under reflux for 5 hours. After cooling to room temperature, hydrazine (2ml) was added and heated under reflux for 4 hours. After cooled down to room temperature, the contents were removed from flask and washed with 5% NaHCO_3 solution (50ml) and deionized water (2x50ml). The solvent was dried over anhydrous magnesium sulfate and removed under reduced pressure. The crude crystals were purified by recrystallized from hexane to give pure product with an isolated yield of 93% (5.3 g, 0.0213 mol), mp = 126-127 °C (lit mp = 127-128 °C)⁷.



The synthesis of 4,4,5,5-tetramethyl-3-phenyl-1-(toluene-4-sulfonyl)-4,5-dihydro-1H-pyrazole (5a)

The following procedure is a representative of **5a**. 4,4,5-trimethyl-3-phenyl-4H-pyrazole (**2a**) (2.0 g, 10.73 mmol) was dissolved in anhydrous THF (120ml) in a 250ml three neck round bottom flask with a magnetic stir bar. The solution was purged with argon gas and brought down to 0°C with an ice bath. Methyl lithium (8.05 ml, 12.88 mmol, 1.2 mol Eq.) was added to the solution and stirred for 30 minutes at 0°C. Then removed the ice bath and stirred the solution for 2 additional hours at room temperature. Then a solution of p-toluenesulfonyl fluoride (3.741 g, 21.47 mmol, 1.2 mol Eq.) in dry THF (10ml) was added to the reaction flask using a glass syringe. The solution was stirred for 3 hours at room temperature. Then the reaction was quenched with 15ml of saturated, degassed ammonia chloride solution. Diethyl ether (30ml) was added to the flask before extraction. The content was washed with saturated sodium bicarbonate (2x50ml) and with dionized water (50ml). The organic layer was separated and dried over magnesium sulfate. The solvent was removed under reduce pressure. The crude product was purified by flash chromatography (hexane: ethyl acetate [90:10]) with an isolated yield of 39% (1.49g, 4.18 mmol),

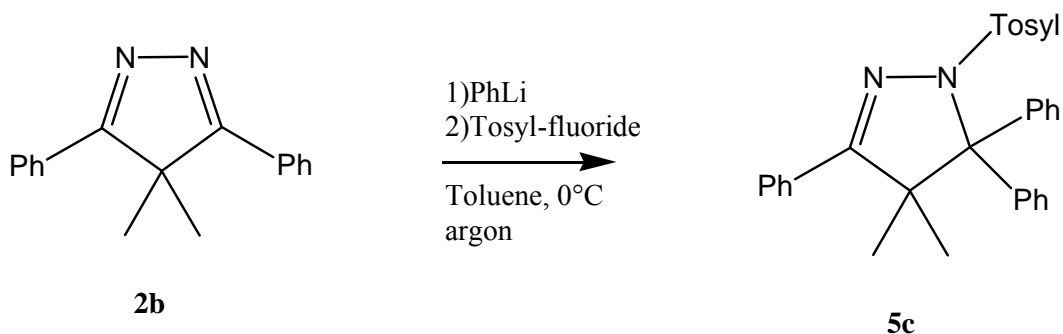
mp = 113-114°C; ¹H NMR (CDCl₃) 300MHz: δ 1. 17 (s, 6H), δ 1. 32 (s, 6H), δ 2. 41 (s, 3H), δ 7. 27 –7. 96 (m, 9H); ¹³C NMR (CDCl₃) 300MHz: 20. 2, 20. 4, 21. 5, 53. 5, 75. 1, 127. 4, 128. 2, 128. 3, 129. 2, 129. 6, 131. 5, 137. 4, 143. 4, 161. 9;
Anal. Calcd. for C₂₀H₂₄N₂O₂S: C, 67. 38; H, 6. 79; N, 7. 86%. Found: C, 67. 33; H, 6. 70; N, 7. 78%.



Synthesis of 4,4,5-Trimethyl-3,5-diphenyl-1-(toluene-4-sulfonyl)-4,5-dihydro-1H-pyrazole (**5b**)

The following procedure is a representative of **5b**. 4,4-Dimethyl-3,5-diphenyl-4H-pyrazole (**2b**) (2. 0 g, 8. 06mmol) of was dissolved in 100 ml of anhydrous THF in a 200ml three neck round bottom flask with a magnetic stir bar. The solution was purged with argon gas and brought down to 0°C with an ice bath. Methyllithium (6. 14 ml, 9. 84mmol, 1. 2 mol Eq.) was added to the solution and stirred for 30 min at 0°C. Then removed the ice bath and stirred the reaction for 1 additional hour at room temperature. Then a solution of p-toluenesulfonyl fluoride (1. 7g, 9. 84mmol, 1. 2 mol Eq.) in dry THF (10ml) was added to the reaction flask at 0°C, using a glass syringe. The solution was stirred for 3 hours at room temperature. The reaction was quenched with 15ml of saturated, degassed ammonia chloride solution. Diethyl ether (30ml) was added

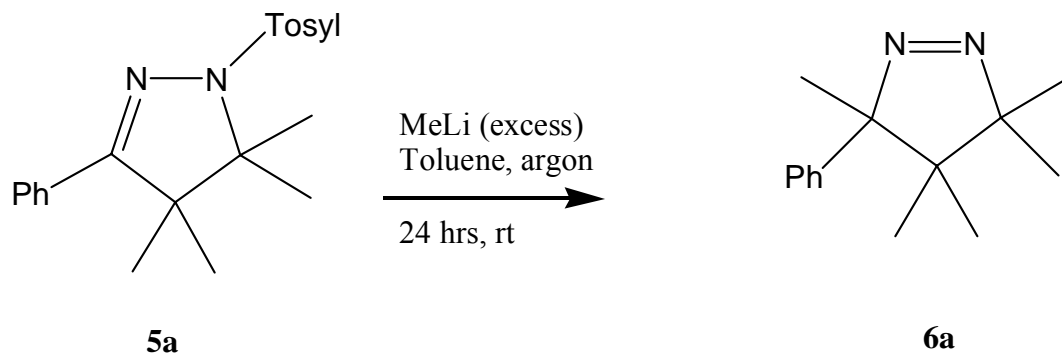
to the flask before washing. The content was washed with saturated sodium bicarbonate (2x50ml) and with dionized water (50ml). The organic layer was separated and dried over magnesium sulfate. The solvent was removed under reduce pressure. The crude product was recrystallized from ethanol and gave an isolated yield of 91% (3.05 g, 7.29mmol), mp = 169-170°C; ^1H NMR (CDCl_3) 300MHz: δ 0.78 (s, 3H), δ 1.26 (s, 3H), δ 1.72 (s, 3H), δ 2.42 (s, 3H), δ 7.27 – 7.92 (m, 14H); ^{13}C NMR (CDCl_3) 300MHz: 19.2, 20.3, 21.6, 24.1, 55.5, 80.5, 126.8, 127.5, 127.63, 127.69, 128.4, 128.5, 129.1, 129.6, 131.5, 137.3, 139.4, 143.5, 161.2; ms: M+1 418; IR peaks: 679cm^{-1} , 1153cm^{-1} , 1331cm^{-1} , 1598cm^{-1} ; *Anal.* Calcd. for $\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_2\text{S}$: C, 71.74; H, 6.26; N, 6.69%. Found: C, 71.79; H, 6.44; N, 6.71%.



The synthesis of 4,4-dimethyl-3,5,5-triphenyl-1-(toluene-4-sulfonyl)-4,5-dihydro-1H-pyrazole (**5c**)

The following procedure is a representative of (**5c**). 4,4-Dimethyl-3,5-diphenyl-4H-pyrazole (**2b**) (1.0 g, 4.03mmol) of was dissolved in 100 ml of anhydrous THF in a 200ml three neck round bottom flask with a magnetic stir bar. The solution was purged with argon gas and brought down to 0°C with an ice bath. Phenyllithium (4ml, 8.06mmol, 2 mol Eq.) was added to the solution

and stirred for 30 min at 0°C. Then removed the ice bath and stirred for 24 hours at room temperature. Then a solution of p-toluenesulfonyl fluoride (1.39g, 8.06 mmol, 2 mol Eq.) in dry THF (10ml) was added to the reaction flask using a glass syringe. The solution was stirred for 3 hours at room temperature. The reaction was quenched with 15ml of saturated, degassed ammonia chloride solution. Diethyl ether (30ml) was added to the flask before washing. The content was washed with saturated sodium bicarbonate (2x50ml) solution and deionized water (50ml). The organic layer was separated and dried over magnesium sulfate. The solvent was removed under reduced pressure. The crude product was purified by recrystallized from acetone and ethyl acetate to give an isolated yield of 51% (0.98 g, 2.056mmol), mp = 240-242°C; ¹H NMR (CDCl₃) 300MHz: δ 1.12 (s, 6H), δ 2.31 (s, 3H), δ 6.89–7.76 (m, 19H); ¹³C NMR (CDCl₃) 300MHz: 21.4, 24.0, 56.5, 86.9, 127.0, 127.7, 127.8, 128.9, 128.3, 128.6, 129.8, 130.7, 135.6, 136.8, 142.5, 161.4; *Anal.* Calcd. for C₃₀H₂₈N₂O₂S: C, 74.97; H, 5.87; N, 5.83%. Found: C, 75.05; H, 5.82; N, 5.58%.

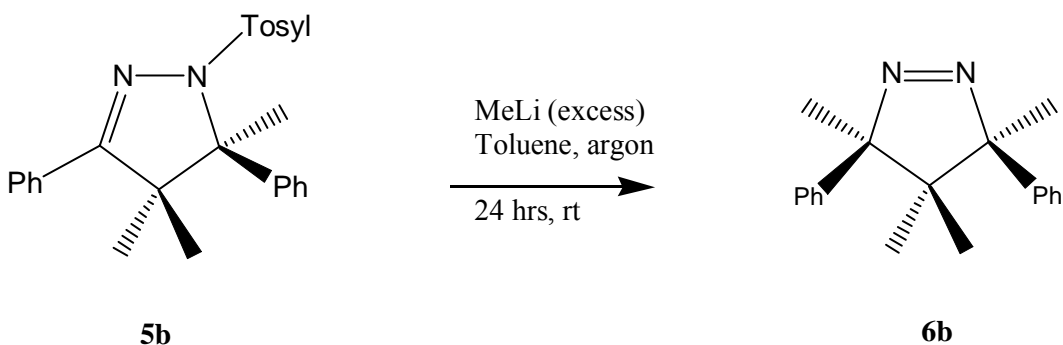


Synthesis of 3,3,4,4,5-pentamethyl-5-phenyl-4,5-dihydro-3H-pyrazole (6a)

The following procedure is a representative for **6a**. 4,4,5,5-tetramethyl-3-phenyl-1-(toluene-4-sulfonyl)-4,5-dihydro-1H-pyrazole (**5a**) (0.30 g, 0.8415 mmol) was dissolved in anhydrous toluene (25 ml), under argon atmosphere. The solution was brought down to 0°C with an ice bath. Then methyllithium (2ml, 3.2mmol, 3.8 mole Eq.) was added to the solution using a dried glass syringe. The solution was stirred for 30 minutes at 0°C and 24 additional hours at room temperature. Then the reaction was quenched with 10 ml of saturated, degassed ammonium chloride solution. Diethyl ether (20ml) was added to the reaction before washing. The reaction was washed with saturated sodium bicarbonate (2x20ml) solution and deionized water (30ml). The organic layer was dried from magnesium sulfate. The solvent was removed under reduce pressure. The crude product was purified by flash chromatography (hexane/ethyl acetate [95:5]) and gave an isolated yield of 87% (0.158g, 0.732 mmol). **6a** is a clear and viscous liquid; ¹H NMR (CDCl₃) 300MHz: δ 0.34 (s, 3H), δ 1.07 (s, 3H), δ 1.30 (s, 3H), δ 1.35 (s, 3H), δ 1.60 (s, 3H), δ 7.25-7.36 (m, 5H); ¹³C NMR (CDCl₃) 300MHz: 20.5, 23.9, 23.9, 24.1, 25.1, 41.8, 91.7, 96.0, 125.5,

126. 8, 128. 0, 143. 8; Exact Mass *Anal.* Calcd. for C₁₄H₂₁N₂ = 217. 17047.

Found: 217. 17060.

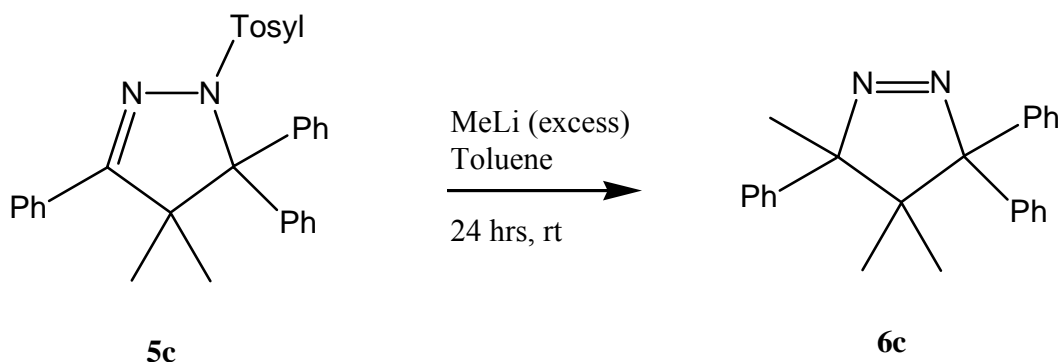


Synthesis of *cis*-3,4,4,5-tetramethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole

(6b)

The following procedure is a representative for **6b**. 4,4,5-Trimethyl-3,5-diphenyl-1-(toluene-4-sulfonyl)-4,5-dihydro-1H-pyrazole (**5b**) (1. 0 g, 2. 389 mmol) of was dissolved in 50 ml of anhydrous THF, under argon atmosphere. The solution was brought down to 0°C with an ice bath. Then methyllithium (4. 48ml, 7. 17mmol, 3 Eq.) was added to the solution using a dried glass syringe. The solution was stirred at 0°C for 30 minutes and 24 additional hours at room temperature. The reaction was quenched with 10 ml of saturated, degassed ammonium chloride solution. Diethyl ether (20ml) was added to the reaction before washing. The reaction was washed with saturated sodium bicarbonate (2x40ml) solution and dionized water (40ml). The organic layer was dried over magnesium sulfate. Solvent was removed under reduce pressure. The crude product was purified by flash chromatography (hexane/ethyl acetate [97:3]) and gave an isolated yield of 59% (0. 391g, 1. 409 mmol), mp = 144-145°C; ¹H NMR (CDCl₃) 300MHz: δ -0. 26 (s, 3H), δ 1. 34 (s, 3H), δ 1. 68 (s, 6H), δ 7. 25-7. 36

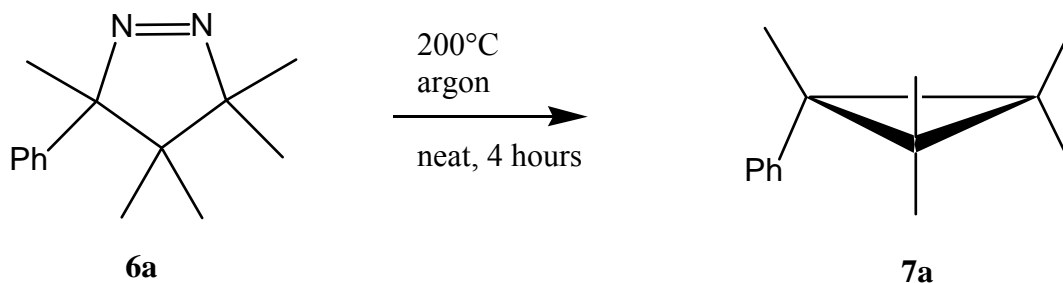
(m, 10H); ^{13}C NMR (CDCl_3) 300MHz: 20. 2, 23. 9, 28. 5, 42. 9, 96. 7, 125. 3, 126. 9, 128. 1, 143. 6; IR peaks: 3064 cm^{-1} , 2990 cm^{-1} , 1599 cm^{-1} , 1560 cm^{-1} , 703 cm^{-1} ; *Anal.* Calcd. for $\text{C}_{19}\text{H}_{22}\text{N}_2$: C, 81. 97; H, 7. 97; N, 10. 06%. Found: C, 81. 70; H, 8. 19; N, 9. 66%.



Synthesis of 3,4,4-trimethyl-3,5,5-triphenyl-4,5-dihydro-3H-pyrazole (6c)

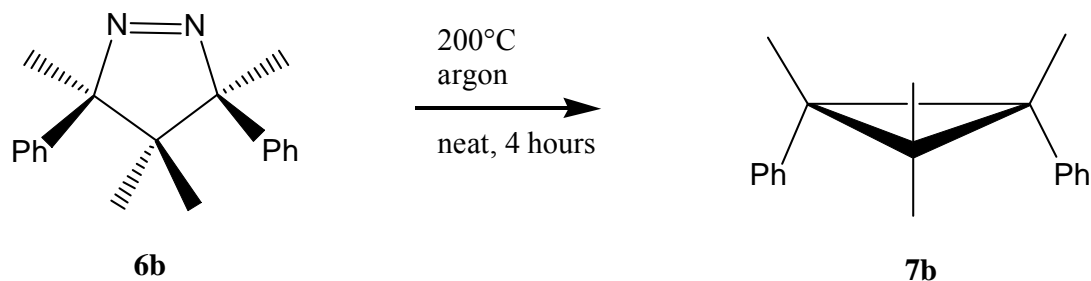
The following procedure is a representative for **6c**. 4,4-dimethyl-3,5,5-triphenyl-1-(toluene-4-sulfonyl)-4,5-dihydro-1H-pyrazole (**5c**) (0. 5 g, 1. 040 mmol) was dissolved in anhydrous THF (50 ml), under argon atmosphere. The solution was brought down to 0°C with an ice bath. Then methyllithium 2. 6ml (4. 16mmol, 4 Eq.) was added to the solution using a dried glass syringe. The solution was stirred for 30 minutes at 0°C and 36 additional hours at room temperature. The reaction was quenched with 10 ml of saturated, degassed ammonium chloride solution. Diethyl ether (20ml) was added to the reaction before washing. The reaction was washed with saturated sodium bicarbonate (2x40ml) solution and dionized water (40ml). The organic layer was dried over magnesium sulfate. Solvent was removed under reduce pressure. The crude product was purified by chromatotron (hexane/ethyl acetate) to gave an isolated yield of 55% (0. 19g, 0. 558 mmol), mp = $117\text{-}118^\circ\text{C}$. ^1H NMR (CDCl_3)

300MHz: δ 0.15 (s, 3H), δ 1.16 (s, 3H), δ 1.56 (s, 3H), δ 7.16-7.97 (m, 15H);
 ^{13}C NMR (CDCl_3) 300MHz: 20.7, 21.8, 27.3, 46.6, 96.6, 97.6, 125.7, 126.5,
126.7, 127.0, 127.2, 128.0, 128.1, 142.6, 143.5, 143.9; *Anal.* Calcd. for
 $\text{C}_{24}\text{H}_{24}\text{N}_2$: C, 84.67; H, 7.11; N, 8.23%. Found: C, 84.73; H, 7.19; N, 8.26%.



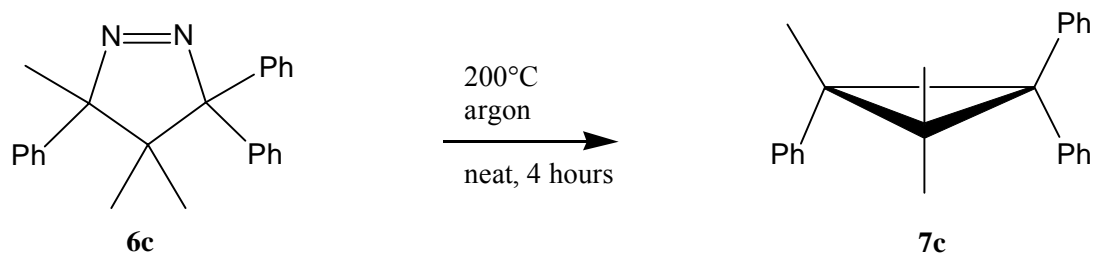
Synthesis of 1,1,2,2,3-pentamethyl-3-phenylcyclopropane (7a)

The following procedure is a representative for **7a**. 3,3,4,4,5-Pentamethyl-5-phenyl-4,5-dihydro-3H-pyrazole (**6a**) (0.1g, 0.462 mmol) was placed in a NMR tube and purged with argon gas. The tube was then heated by a silicon oil bath at $200^\circ\text{C} \pm 2$ for 4 hours. When the viscous liquid was heated, bubbles of N_2 gas were observed. The NMR tube was removed from the oil bath after 4 hours of heating and hexane was added to dissolve the products. The product was purified by chromatotron to yielded 93% (0.081g, 0.429mmol) of clear viscous liquid. ^1H NMR (CDCl_3) 300 MHz: δ 0.92 (s, 6H), δ 1.16 (s, 6H), δ 1.23 (s, 3H), δ 7.1-7.3 (m, 5H); (lit. ^1H NMR: δ 0.91 (s, 6H), δ 1.15 (s, 6H), δ 1.23 (s, 3H), δ 7.12 (m, 5H) (Gloss *et al.*, 1966); ^{13}C NMR (CDCl_3) 300 MHz: 18.5, 21.70, 21.74, 23.9, 29.7, 33.6, 125.0, 127.9, 130.7, 146.0.



Synthesis of cis-1,1,2,3-tetramethyl-2,3-diphenylcyclopropane (**7b**)

The following procedure is a representative for **7b**. 3,4,4,5-Tetramethyl-3,5-diphenyl-4,5-dihydro-3H-pyrazole (**6b**) (0.1 g, 0.359 mmol) was placed in a NMR tube and purged with argon. The tube was then heated by a silicon oil bath at $200^{\circ}\text{C} \pm 2$ for 4 hours. When heated, the crystals dissolved and bubbles of N_2 gas were observed in the liquid phase. The NMR tube was removed from the oil bath after 4 hours of heating and added hexane to dissolve the product. The product was separated by chromatotron and recrystallized with methanol to give 84% yield (0.075 g, 0.301 mmole) of colorless crystals, mp = $(79-81)^{\circ}\text{C}$. ^1H NMR (CDCl_3) 300 MHz: δ 1.12 (s, 3H), δ 1.37 (s, 3H), δ 1.47 (s, 6H), δ 7-7.4 (m, 10H); ^{13}C NMR (CDCl_3) 300 MHz: 18.7, 23.2, 25.4, 27.0, 35.5, 125.3, 127.4, 131.1, 145.6; X-ray structure was obtained at Emory University; IR peaks: $3083-2927\text{ cm}^{-1}$, 1599 cm^{-1} , 1577 cm^{-1} , 699 cm^{-1} .



Synthesis of 1,1,2-trimethyl-2,3,3-triphenylcyclopropane (7c)

The following procedure is a representative for 7c. 3,4,4-Trimethyl-3,5,5-triphenyl-4,5-dihydro-3H-pyrazole (6c) (0.1 g, 0.2937 mmol) was placed in a NMR tube and purged with argon. The tube was then heated by a silicon oil bath at $200^{\circ}\text{C} \pm 2$ for 4 hours. When heated, the crystals dissolved and bubbles of N_2 gas were observed in the liquid phase. The NMR tube was removed from the oil bath after 4 hours of heating and added hexane to dissolve the products. The product was purified by chromatotron to give 91% yield (0.83 g, 0.267 mmol) of colorless viscous liquid. ^1H NMR (CDCl_3) 300 MHz: δ 1.32 (s, 3H), δ 1.33 (s, 3H), δ 1.38 (s, 3H), δ 6.9-7.6 (m, 15H); ^{13}C NMR (CDCl_3) 300 MHz: 22.2, 26.8, 27.2, 28.1, 37.9, 46.2, 125.0, 125.3, 125.5, 127.5, 127.9, 128.1, 131.0, 131.3, 143.9, 144.3, 144.4; Exact mass anal, calcd. for $\text{C}_{24}\text{H}_{24}$ = 312.18780; Found: 312.19317

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