STUDY OF HETEROAROMATIC ENEDIYNE AND SUBSTITUTED BENZOTHIOPHENE SYNTHESIS WITH RELATIVE REACTIVITY OF SUBSTITUTED ARYL IODIDES IN THE SONOGASHIRA REACTION

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By

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ABSTRACT

STUDY OF HETEROAROMATIC ENEDIYNE AND SUBSTITUTED BENZOTHIOPHENE SYNTHESIS WITH RELATIVE REACTIVITY OF SUBSTITUTEDARYL IODIDES IN THE SONOGASHIRA REACTION

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Enediyne compounds have captured the imagination of chemists since their discovery as a class of natural products. Because of their cytotoxicity, these compounds are not suitable for use in cancer treatment. As a result, chemists have aimed to reduce their toxicity, improve stability and elucidate the mechanism of their cyclization reaction. The Sonogashira coupling reaction is used to synthesize a number of heteroaromatic enediynes and has been examined. By coupling a number of alkynes with 2,3-dibromothiphene a number of corresponding disubstituted enediynes were produced. In order to get fused bicyclic heteroaromatic products both thermal and photochemical Bergman cyclizations have been performed with these enediynes. To date, the attempted cyclizations have not been successful.

Beside this, a series of competitive reactions was carried out to determine the relative reactivity of substituted aryl iodides in the Sonogashira reactions. These reactions were carried out in co-catalyst system composed of Pd/CuI. The competitive reactions between iodobenzene and a number of 3- and 4-substituted iodobenzenes provided relative rates which were compared to the theoretical electron densities of the iodide-bearing carbon. Generally, electron withdrawing substituents in the *para-* and *meta-* positions increased the reactivity, while donating substituents decreased the rate of reaction. It was found that resonance effects have a greater effect on reactivity than inductive effects.

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LIST OF ABBREVIATIONS

DNA	Deoxyribonuclic Acid
GC	Gas Chromatography
GLC	Gas Liquid Chromatography
GC-MS	Gas Chromatography Mass-Spectrometry
IR	Infrared
NMR	Nuclear Magnetic Resonance
Et	Ethyl
Me	Methyl
Pr	Propyl
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
FTIR	Fourier Transform Infrared
cd	Carbon Distance
Et_3N	Triethylamine
FID	Flame Ionization Detector
hv	Light
MS	Mass Spectrometry
ppm	parts per million
R_f	Retardation Factor
RT	Retention Time

SERM	Selective Estrogen Receptor Modulator
TEMPO	2,2,6,6-tetramethyl-1-piperdinyloxy
Δ	Heat
HRT	Hormone Replacement Therapy
MO	Molecular Orbital
HOMO	Highest Occupied Molecular Orbital
LUMO	Lowest Unoccupied Molecular Orbital

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CHAPTER ONE

A SYNTHETIC AND MECHANISTIC REVIEW OF ENEDIYNE CHEMISTRY

1.1 Introduction

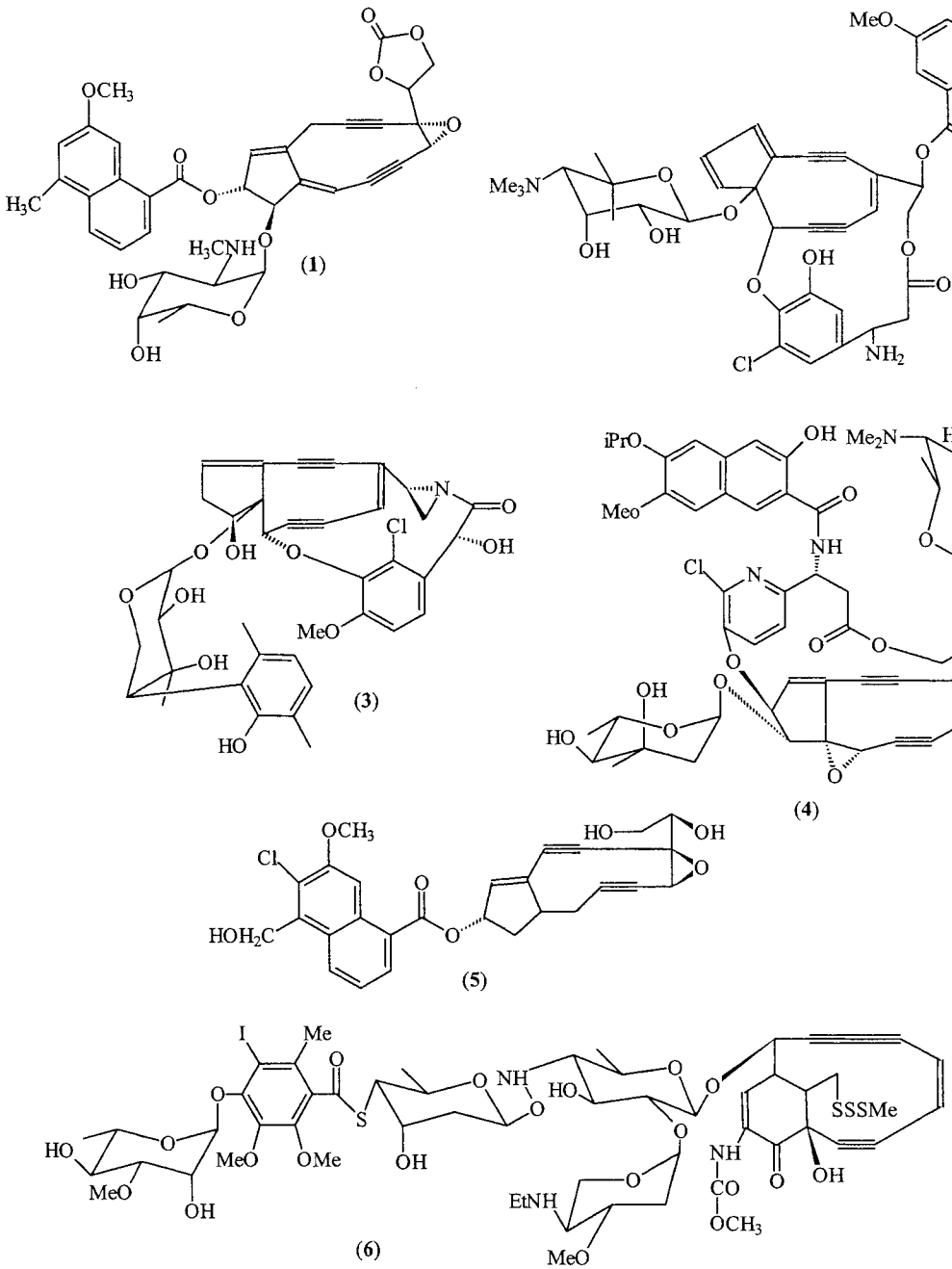
Man's fascination with natural products goes back to ancient times. With the discovery of Salicin from willow tree extracts and the development of aspirin in 1899, the art of exploiting natural products became a molecular science. The discovery of a class of compounds called the enediynes in the mid 1980's and its subsequent drug development represented another milestone in the history of natural products, and marked the beginning of a new chapter in drug discovery, in which bacteria were added to the plant kingdom as a source of biologically active compounds. Indeed, a large portion of today's major drugs have their origin in nature. Interest in enediynes has grown because of their anticancer activity;[1] this class of naturally occurring compounds can selectively cleave DNA. However, enediynes are toxic, and some of them are unstable for biological application. Researchers are currently trying to synthesize and develop analogues, and to investigate mode of action in order to better control their activity. The goal of many researchers is to prepare enediynes, using a synthetically simple strategy, that contain an active site that could be activated in a controlled manner.

In this thesis, reviews of anticancer agents and the bicyclic heteroaromatic fused ring systems will be presented, followed by reviews of synthetic methodology most commonly used in enediyne synthesis and reactions under which they can cyclize.

1.2 Classes Of Naturally Occurring Enediynes

Five classes of naturally occurring enediynes are known. The enediyne family of antibiotics (Fig. 1) is characterized structurally by an enediyne core unit consisting of two acetylenic groups conjugated to a double bond or incipient double bond within a 9- or 10-membered ring.[2-4] To date, five unique 9-membered enediynes (**1**–**5**) (Fig. 1), often designated as the chromoprotein enediynes, and five additional distinct naturally occurring 10-membered enediynes (**6**–**10**) (Fig. 1) have been elucidated structurally.[5-7] In general, these enediynes contain three distinct structural elements: a DNA-recognition unit, which serves to deliver the metabolite to its target DNA; an activation component, which sets the stage for cycloaromatization; and the enediyne "warhead," which cycloaromatizes to a highly reactive diradical species and, in the presence of DNA, results in oxidative strand scission of the targeted sequence.[8-10] *In vitro* and *in vivo* studies are consistent with the role of enediynes as DNA-damaging agents and suggest that they may even favour cleavage at certain chromosomal sites and/or tertiary structures.[11,12] Although this extraordinary reactivity invokes incredible potency (some enediynes are >8,000-fold), the enediynes are similar to most cytotoxins in their general lack of tissue specificity. However, targeting via polymer-assisted delivery devices **1**-poly(styrene-maleic acid)-conjugated neocarzinostatin or conjugation to tumor-specific monoclonal antibodies (as in the **6**-based Mylotarg) has led to clinical success.[13]

Figure: 1



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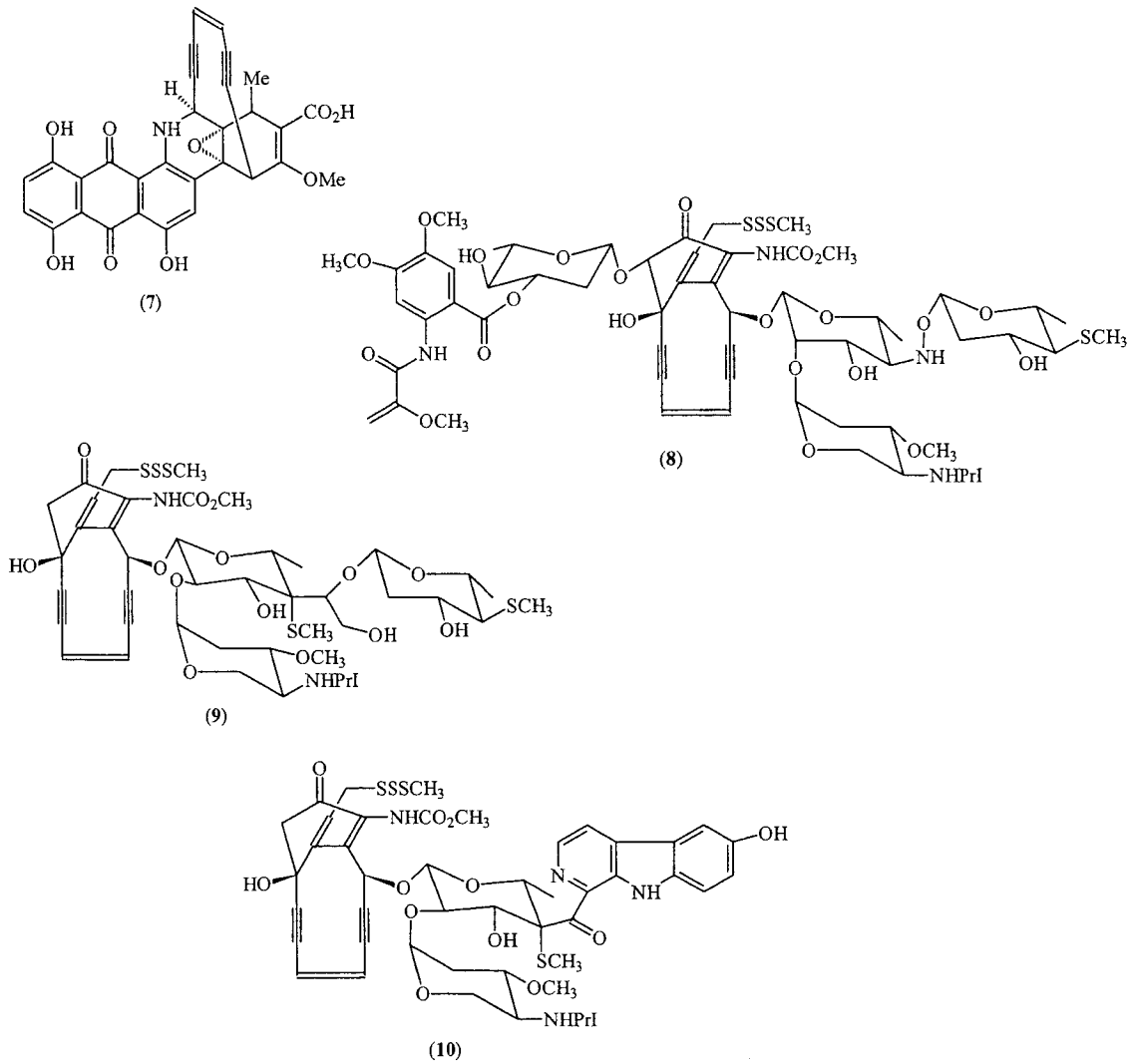
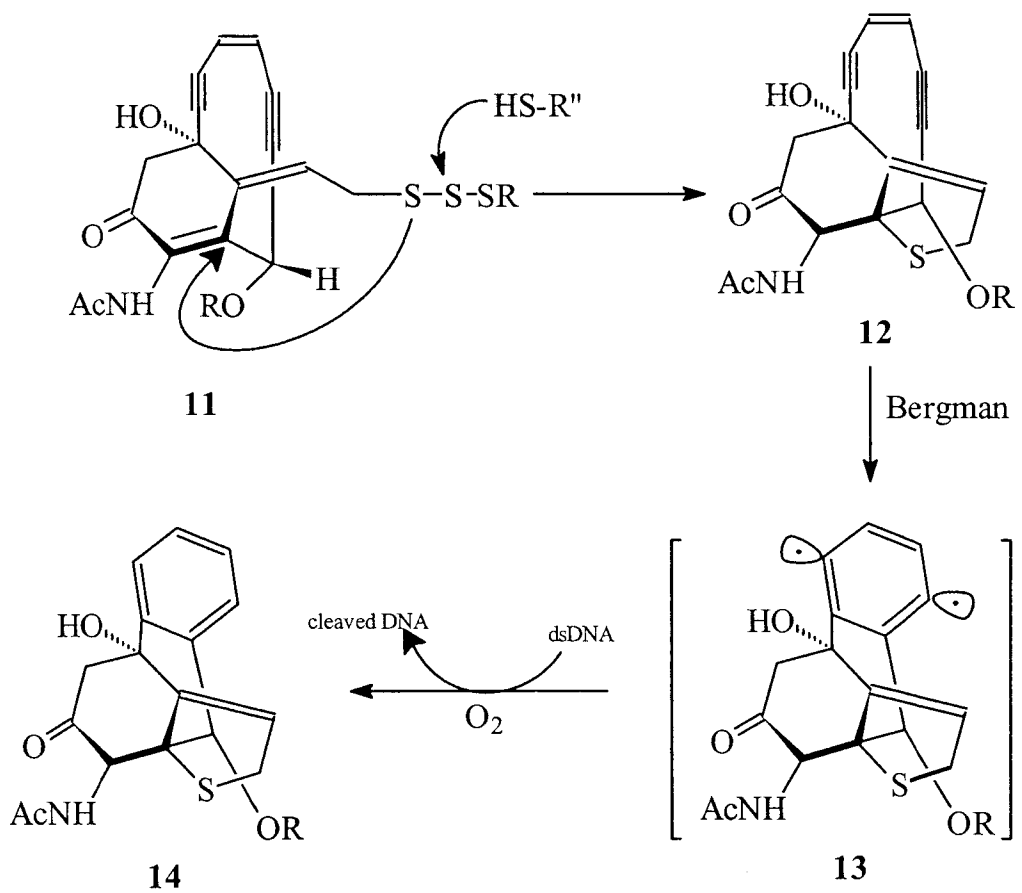


1.3 Mode Of Action

The enediyne group is often called a warhead because it is ready to cyclize, forming benzene via a highly reactive 1,4-benzeniod diradical intermediate. This diradical intermediate is responsible for the oxidative DNA cleavage. This cyclization process is named the Bergman cycloaromatization reaction.[14] The enediyne group readily cyclizes via a diradical intermediate that cleaves the DNA, giving rise to enediynes' powerful antitumor activity. The antitumor activity of enediyne natural products stems

from their ability to cleave double stranded DNA (ds DNA), which induces cell apoptosis.[15] The biological mode of action occurs along one of two general pathways, depending the type of enediyne structure (Scheme **1**). The majority of enediynes undergo Bergman cyclization.[14] The sequence that leads to this cyclization begins when a cellular thiol, such as glutathione attacks the trisulfide bond, liberating a thiolate which then reacts with the unsaturated enone via 1,4- addition. The resulting rehybridization of the bridgehead carbon (sp^2 to sp^3) induces a conformational change that decreases the distance between diyne termini in **12**.

Scheme 1



The Bergman cyclization now proceeds readily to afford the *p*-benzyne diradical **13** that abstracts two hydrogen atoms, one each from the opposite strands of a complementary base pair producing the arene **14.**[15] The chemical consequences of these hydrogen atom abstractions lead to double-stranded DNA cleavage, which induces apoptosis.[15]

There are four principle effects of the enediynes on the cell: 1. Mutagenicity; 2. Antimitotic activity associated with cell-cycle arrest; 3. Apoptosis induction; and 4. Differential induction. Mutagenicity, the capacity to induce mutations, of enediynes has been shown to be sulf-hydryl dependent and varies with concentration, which is proportional to the cytotoxicity. That is, as the surviving fraction of cells diminishes, there is an increase of the percentage of remaining cells with a mutant phenotype. Enediynes act as antimitotic agents by inducing a temporary delay in division. Mitosis is a process that takes place in the nucleus of a dividing cell, involves typically a series of steps consisting of prophase, metaphase, anaphase, and telophase, and results in the formation of two new nuclei each having the same number of chromosomes as the parent nucleus. Cell growth remains blocked for some period of time, usually one hour, demonstrating a decrease in the mitotic index. The antimitotic effect is irreversible. Stable, designed enediynes appear to block apoptosis induction (genetically determined destruction of the cell by internal stimulation). Competitive inhibitors, such as receptor-ligand-like interactions, are not universally seen in natural enediynes. The determination of whether a particular cell undergoes apoptosis or differentiation is a function of the endogenous properties of that cell rather than the concentration or nature of the enediyne.

All of the enediyne antibiotics were originally derived by fermentation of microorganisms. The various species organisms produced different enediyne complexes.

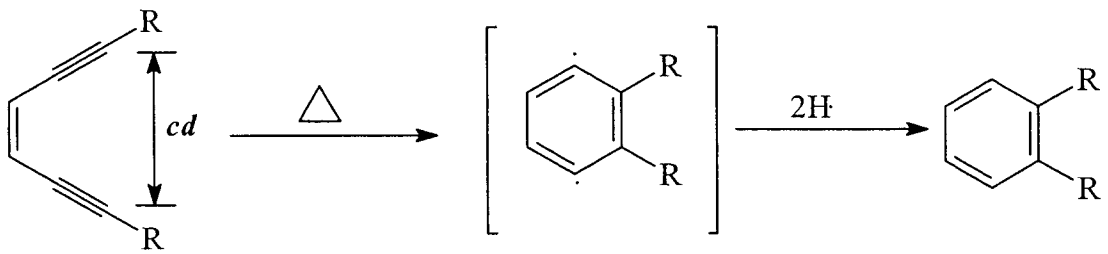
1.4 Cycloaromatization

The enediynes remain among the most potent antitumor agents to have been discovered in the past decade.[1] Activation of the enediynes to undergo cycloaromatization reactions results in the formation of highly reactive diradical intermediates. The diradical species engage in atom transfer chemistry to produce neutral arene products, in the process inducing damage to key macromolecules. Several of the naturally occurring members of the enediyne family of antibiotics have entered clinical trials, and this has prompted the design of synthetic enediynes, where the enediyne "warhead" is conjugated to a targeted delivery vehicle. This section of the review will describe recent efforts using chemical synthesis to identify and improve the target specificity of designed enediynes and to establish efficient methods to achieve activation. Finally, new horizons will be examined, including the use of post-cycloaromatized enediyne templates as recognition elements for unique DNA and RNA microenvironments. The Bergman cyclization[14] has received much of attention in the literature since almost all of the natural anticancer agents that have been discovered function through this mechanism. However, there are other cycloaromatization pathways that have been elucidated; those are the Myers-Saito cyclization,[16] the Schmittel cyclization[17,18] and the Tandem cyclization.[1,19]

1.4.1 Bergman Cyclization

Jones and Bergman reported a reaction which has since been known as the Bergman cyclization[14] in 1972. They reported that enediynes undergo thermal cyclization on heating. Bergman then proposed a mechanism for this cyclization. His proposed mechanism involves a biradical intermediate which could abstract hydrogens from a hydrogen donor source which leads to the final aromatic product (Scheme **2**).

Scheme 2



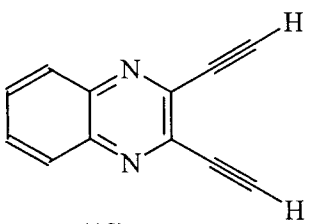
(15) **(16)** **(17)**

Although there is no direct evidence of the existence of biradical, there is indirect evidence such as radical trapping experiments using TEMPO.[20] There are a number of factors which influence the reactivity of enediynes. Nicolaou *et al.* studied a class of enediynes[21] and reported that the reactivity towards Bergman cyclization could be determined by distance calculated and observed between acetylenic carbons (*cd*). It was concluded in their report that distances (*cd*) lower than 3.20Å cyclized spontaneously at all temperatures via the intermediate (Scheme **2**). Enediynes with (*cd*) distance 3.20 to 3.31Å cyclize at 25°C, while distances greater than 3.31Å are stable at 25°C.

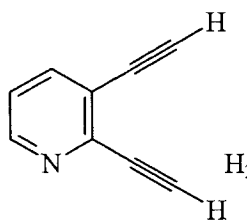
Grissom has found that the addition of one alkyl unit on a terminal carbon increases the activation energy from 25.1 kcal/mol to 28.1 kcal/mol.[22] When a second alkyl unit was added the cyclization barrier was raised to 34.0 kcal/mol. It was concluded that the thermal stability of enediyne was a direct result of *cd* alone. The limitations of Nicolaou's conclusions have been discussed greatly. James P. Snyder has examined a series of reactions and concluded that although *cd* and reactivity of enediynes are related in monocyclic systems, they do not apply consistently to more complex ring systems.[23] In related calculations, the transition state for cyclization was shown to possess 35% biradical character, lending support to Bergman's proposed mechanism. As a result, Snyder proposed that fusion of additional rings introduces competitive strain; these compounds do not benefit from the diminished kinetic barriers enjoyed by shorter *cd* in monocyclic systems.[23]

Magnus *et al.* conducted kinetic studies on enediynes to correlate between strain energy and its reactivity.[24] They concluded that the cyclization rates of enediynes are influenced by strain-energy modulation in the pseudocyclic transition state. From their experimental observation it has been concluded that the rate of cyclization is governed much more strongly by strain energy rather than the proximity of the acetylenic carbon (*cd* distances). Other studies reinforce this conclusion, including an elegant comparison between computer modeled *cd*, rates and strain energy, and those determined by experiment, which found excellent correlation between theoretical and experimental values.[23,25]

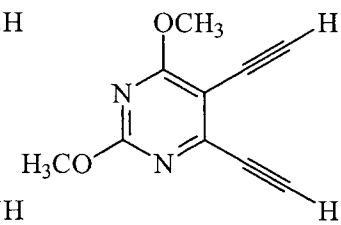
Another factor involved in determining the activity of enediynes to cyclization is the electronic effect. Several aspects of this category have been studied to date, including heteroatomic effects, solvent dependence, aryl ring substitutions, and acetylenic substitutions. In order to investigate how electronic factors influence the rate of cyclization, Kim *et al.* synthesized some aromatic heteroatomic enediynes (**29 - 32**) and did some kinetics experiments.[26]



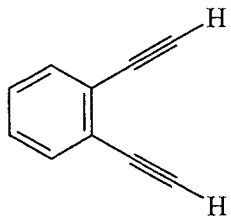
(**18**)



(**19**)



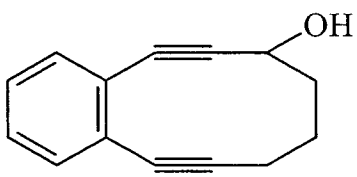
(**20**)



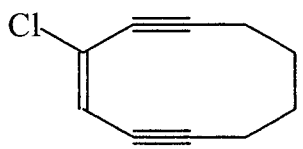
(**21**)

It has been reported that non-aromatic enediynes have shorter half-lives than arenediynes, however, the influence of the double bond has yet to be clarified.[25] Kim *et al.* concluded in their report that electron-withdrawing substituents associated with the double bond tend to increase the Bergman cyclization. The synthesized enediynes (**18 - 21**) were used to measure their respective activation energy utilizing an Arrhenius relationship (rate of disappearance of enediyne versus time). The measured activation energy was compared to analogous nonheteroatomic enediynes (**21**). Compounds **19** and **20** were found to have decreased activation energies compared to **21**. Enediyne **20** was found to be the most reactive acyclic arenediyne studied to date. It was determined that the activation energy of the enediyne increased due to the addition of the aromatic ring in compound **18** relative to **21**.[26] If electron-withdrawing groups are attached to a proximal

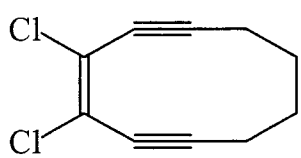
position to the propargylic carbon **22**, there appears to be a rate accelerating effect.[27] Vinyl substitution has also been studied and the results appear to indicate that electron-withdrawing groups lower the rate of reaction by increasing activation energy (**22**, **23**, **24**).[22,28] Numerous studies[25,29-31] have been employed on benzannulated enediynes (**25**) and they found that the nature of double bond has little to no effect on reaction rate , although it may cause a change to rate limiting step.[25,32] During the observation of these experiments, cyclized products were formed in better yields with less polar solvents, and the half-lives were found to correlate linearly with dielectric constants and $E_T(30)$ values.[21,26] This observation is intriguing because it has been reported that cyclization of similar enediynes is solvent independent. More study is necessary to examine whether this phenomenon is general for cyclizations.



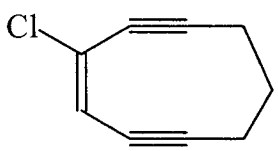
(**22**)



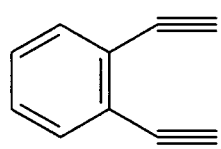
(**23**)



(**24**)



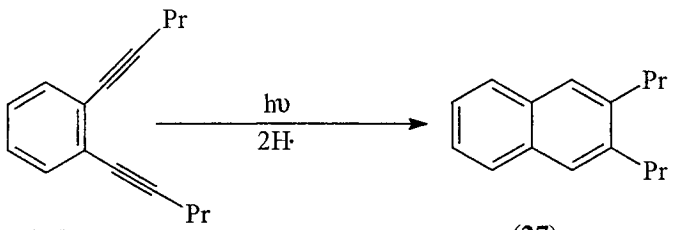
(**25**)



(**21**)

In 1994 Turro *et al.* reported the Bergman photochemical cyclization of **26**.[33] They irradiated this compound in a number of solvents and the product (**27**) formed was the expected Bergman cyclization product (Scheme **3**). This was further evidence of the formation of a biradical intermediate.

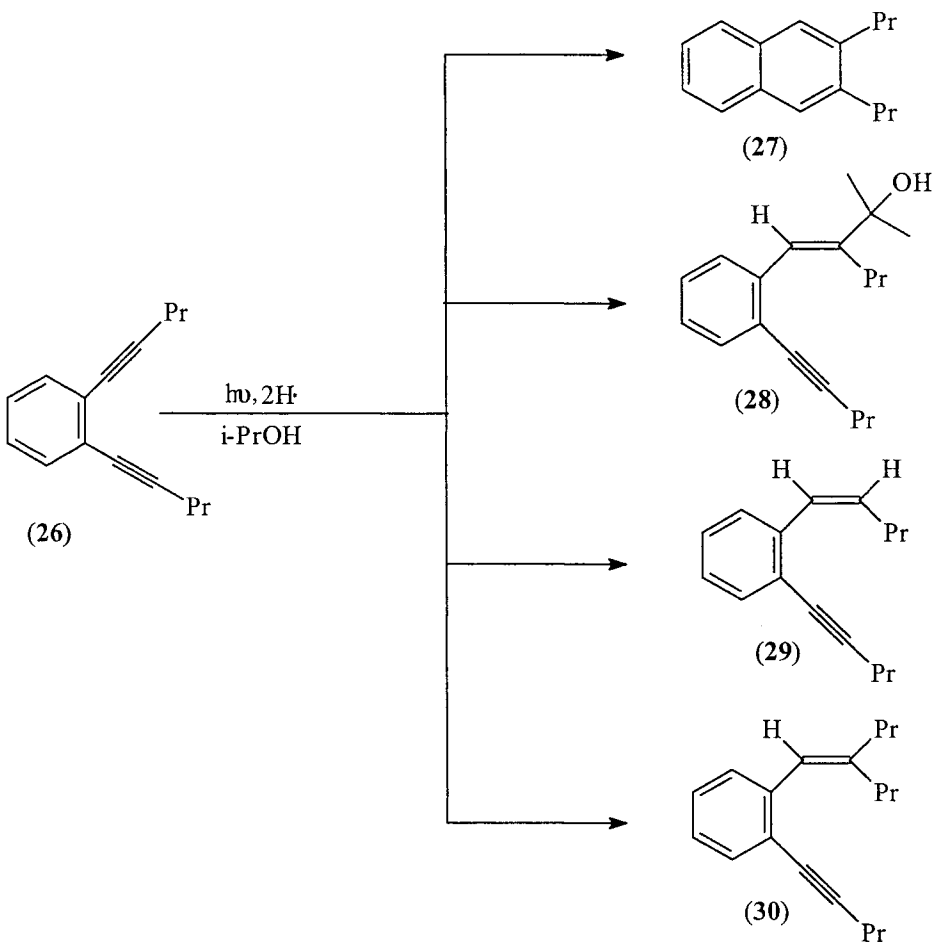
Scheme 3



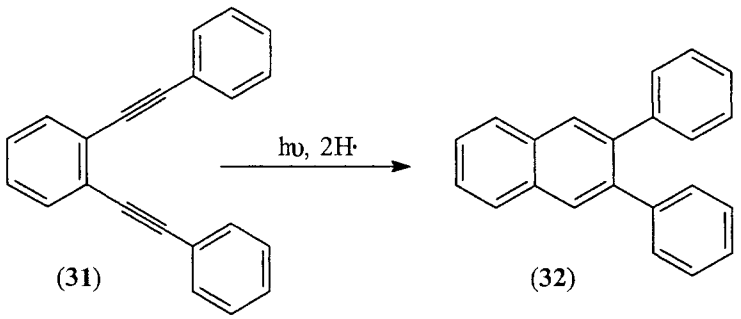
(**26**) (**27**)

A further successful report on Bergman photochemical cyclization has been presented by the same group but with a more in-depth study of their previous results.[34] Different kinds of products were found on cyclization of **26**, one of which was Bergman cyclization product **27**, others being various photoreduction products (**28-30**) (Scheme **4**). The cyclization of **31** yields only Bergman cyclization product **32** (Scheme **5**).

Scheme 4



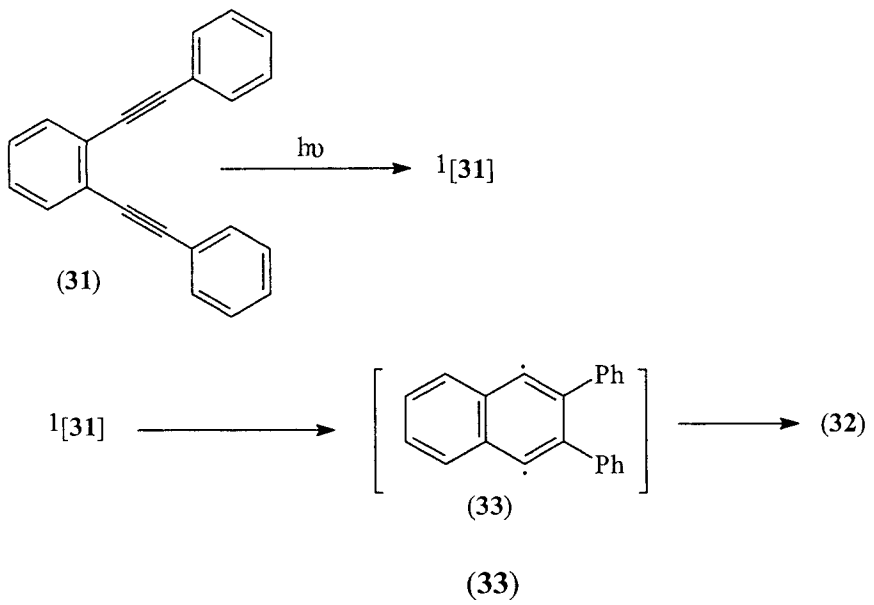
Scheme 5



(31) (32)

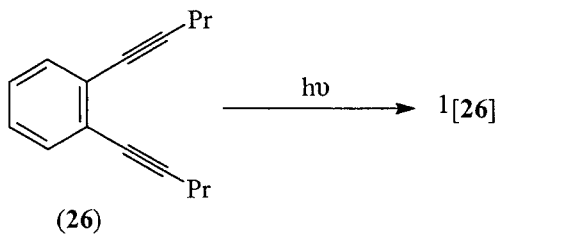
A mechanism was proposed for this cyclization in order to explain the various types of products what were formed in the cyclization reaction. It was suggested that the cyclization occurs from the singlet excited state and that photoreduction occurs from the triplet excited state. This assumption is based on the theory that the quantum yield of fluorescence depends on the rigidity of the molecule.[35] If rigidity is decreased, the chance of other modes of deactivation, such as intersystem crossing, is higher. In **31** two benzene groups make the compound more rigid which prevents intersystem crossing from the first excited singlet state to the first excited triplet state. Since photoreduction occurs from the triplet state, only **32** forms (Scheme **6**). Since **26** is less rigid, intersystem crossing is more likely, allowing for more photoreduction to occur (Scheme **7**).

Scheme 6



(33)

Scheme 7



^{1}[26] ⟶ (27)

^{1}[26] ⟶ ^{3}[26]

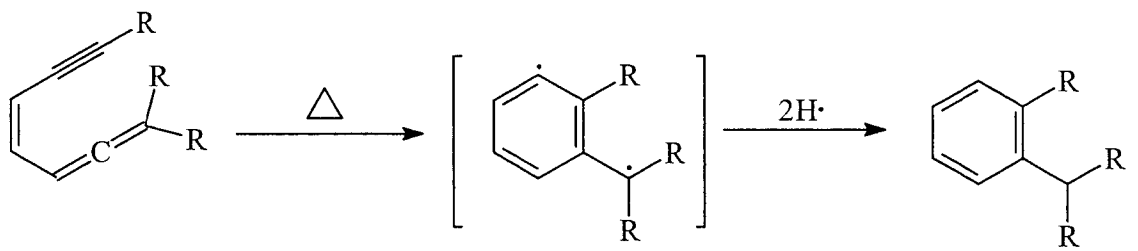
^{3}[26] ⟶ (28) + (29) + (30)

1.4.2 Myers-Satio Cyclization

Neocarzinostain chromophore (**1**), does not react through Bergman cyclization but still exhibits the same ability to cleave DNA strands. This is another form of cycloaromatization known as Myers-Satio cyclization which occurs in eneyne-allene

systems **34.**[16] The proposed mechanism is very close to the Bergman cyclization (Scheme **8**). Three major differences have been found between Bergman and Myers-Satio cyclization. Firstly, the Bergman cyclization involves in enediyne system whereas the Myers-Satio cyclization involves reaction of eneyne-allene systems. Secondly, Myers-Satio cyclization goes through a less reactive σ, π-biradical from the eneyne-allene starting material, whereas, the Bergman cyclization has a very reactive σ, σ-radical intermediate. Finally, Bergman cyclizations are moderately endothermic so heating is often required for cyclization to occur but Myers-Satio cyclizations are quite exothermic.[1,15]

Scheme 8

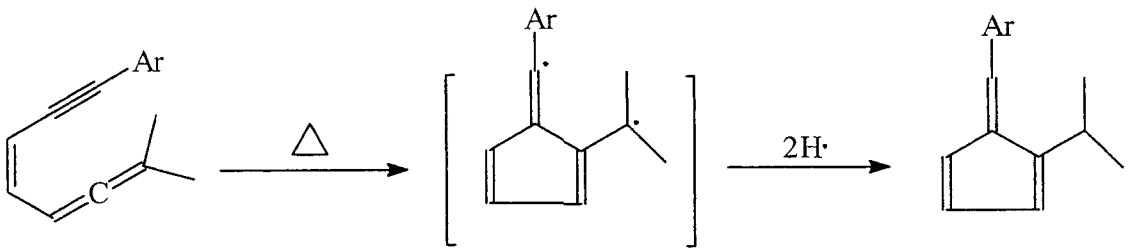


(34) (35) (36)

1.4.3 Schmittel Cyclization

The Schmittel cyclization is typically a Myers-Satio cyclization in which the simple exchange of a hydrogen at the alkyne terminus with an aryl group redirects the thermal reaction mode from the Myers-Satio cyclization to a Schmittel cyclization, resulting in a five-membered rather than six-membered ring (Scheme **9**).[17] The aryl substituents help the reaction to proceed rapidly. The effect of the aryl group is very clear as it stabilizes the radical intermediate which increases the rate of this C2-C6 cyclization.

Scheme 9

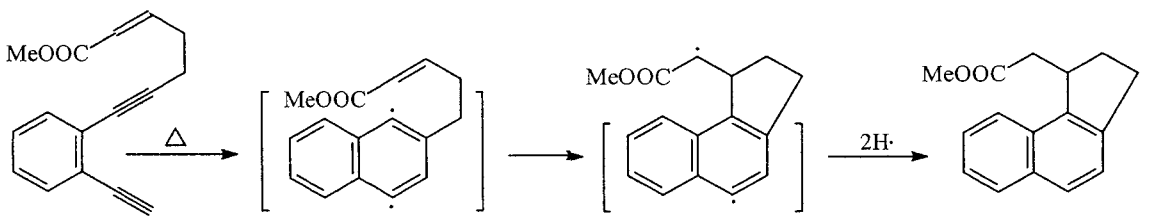


(37) (38) (39)

1.4.4 Tandem Cyclization

Bergman and Myers-Satio cyclization proceed through a biradical intermediate. The intermediate biradical could further react which leads to bi- and polycyclic systems (Scheme **10**).[1, 19] These cyclizations are termed "Tandem cyclizations".

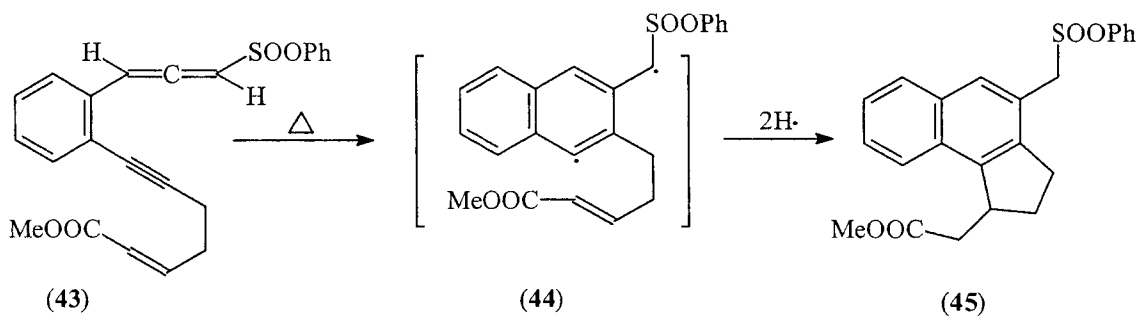
Scheme 10



(40) (41) (41a) (42)

Higher temperatures (150-200°C) are required in this cyclization so sometimes the starting material decomposes. Since Bergman cyclization requires such high temperatures and Myers-Satio cyclization does not, Tandem cyclization has now been performed in enyne-allene systems and may occurred at physiological temperatures (37°C) (Scheme **11**).

Scheme 11



(43) (44) (45)

1.5 Carbon-Carbon Cross Coupling Reactions

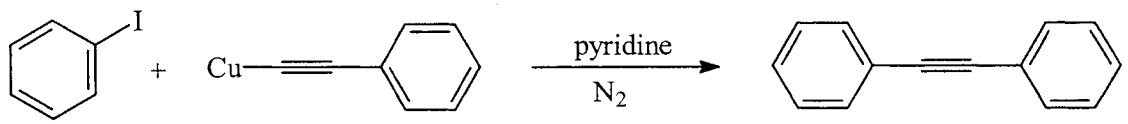
Generally, carbon-carbon cross coupling reactions of vinyl or arylhalides with acetylenes are used to synthesize enediynes and compounds in the formation of benzothiophenes, benzofurans and indoles. They have been investigated since the early 1960's and dramatically improved in recent times.

1.5.1 Stephens-Castro Coupling

Stephens and Castro coupled alkynes with arylhalides in 1963.[36] Synthesized cuprous acetylides undergo a substitution reaction with arylhalides (Scheme **12**). They also studied the reactivity of *para*-substituted iodobenzenes towards coupling with cuprous phenyl acetylide. The trend of reactivity was found to be that I>Br>Cl (fluorides does not react at all). It was observed that the reactions proceeded better if electron-withdrawing groups or poorly electron-donating groups were attached to the arylhalides (NO_2>H>MeO). It was also found that the reaction would not occur if the halogen (leaving group) was not bonded to an sp^2-hybridized carbon. It is very difficult to

synthesize cuprous acetylide and its high degree of instability is the major drawback of this reaction.

Scheme 12



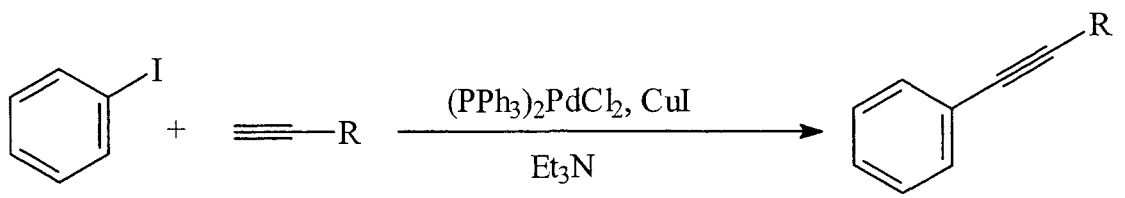
(46) (47) (48)

1.5.2 Sonogashira Coupling

Although the Stephens-Castro coupling procedure was good enough in the formation of desired coupled product, the reactivity of the cuprous acetylides and the extreme conditions required made a milder procedure desirable. This procedure was modified so that cuprous acetylides were generated *in situ*. The modified reaction is the Sonogashira coupling reaction.[37] The classic Sonogashira reaction involves the use of $PdCl_2$, PPh_3, CuI and an amine solvent, generally triethylamine (Scheme **13**). Bromoalkenes, iodoarenes and bromopyridines were coupled with acetylenes at room temperature. The phosphine adds to the palladium metal, allowing for the electronics and the sterics of the catalyst to be adjusted. The role of the amine is to remove acidic material that is produced in the reaction and the role of CuI is not yet completely known. It has been found that the rate of reaction is slow in the absence of CuI and the rate is significantly increased in the presence of CuI.[38,39] Due to the low reactivity of the arylbromides, strong reaction conditions were required to couple arylbromides and terminal alkynes. In order to improve the reactivity, aryliodides were used instead of

arylbromides. The more polarizable C-I bond facilitated higher yields in coupling.

Scheme 13

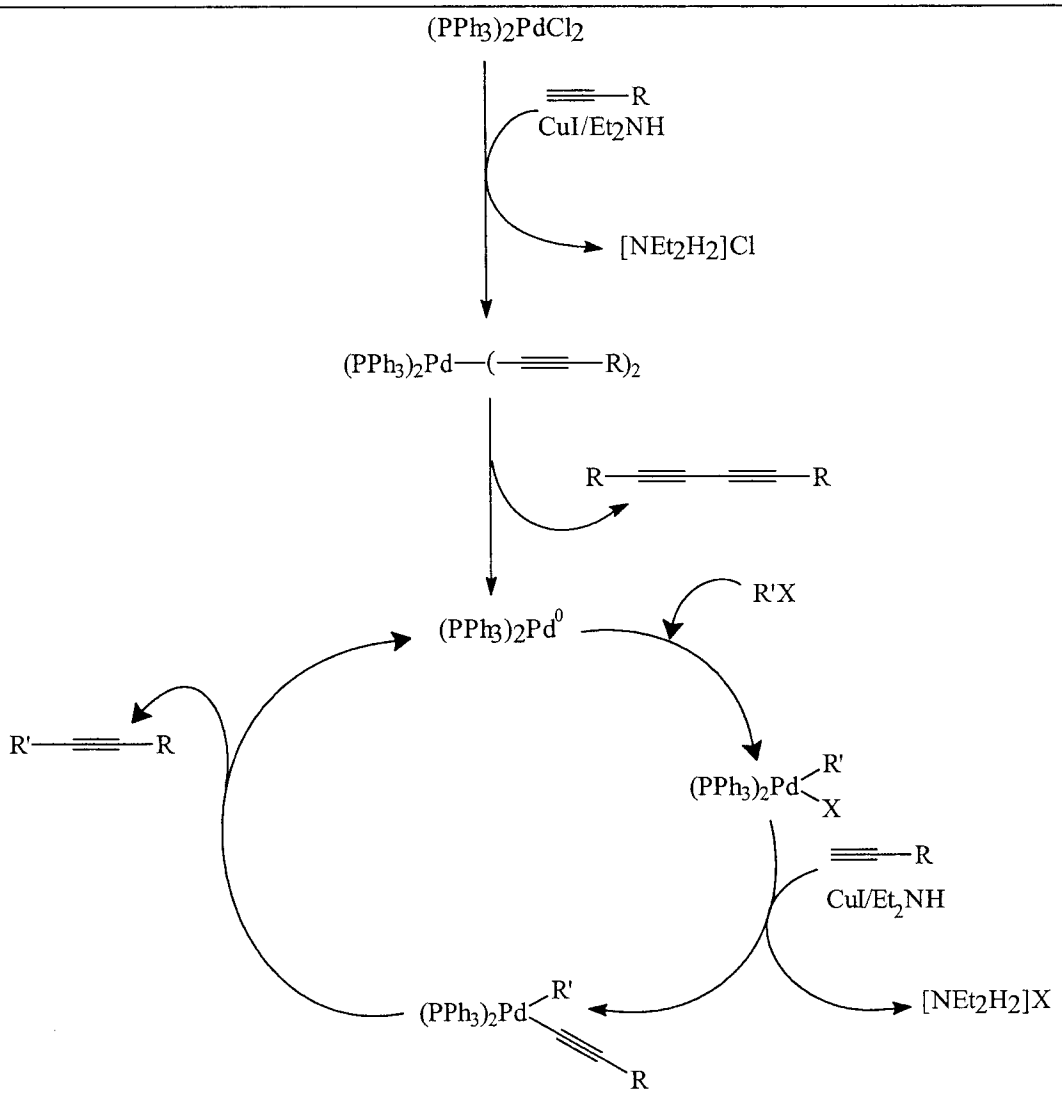


(46) (49)

To date, the mechanism of this reaction has not been elucidated; however, the generally accepted one is that proposed by Sonogashira (Scheme **14**).[37] In his proposed mechanism, Pd(0) is considered an active catalyst, therefore, the first step is a reduction of the pre-catalyst from a Pd(II) state to Pd(0). The catalyst Pd(0) that is generated enters the catalytic cycle and oxidatively adds an aryl or vinyl halide. The oxidative addition is followed by alkylation of the adduct to yield the aryl or vinyl alkynyl complex of palladium. The coupled product is formed by reductive elimination, regenerating the Pd(0) catalyst. It was found that the CuI has a vital role to the progress of reaction; however, this proposed mechanism does not indicate what role it plays in the reaction. The main improvements of this reaction have been made only in the catalyst and solvent. The most common catalysts used are $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$ and Pd/C. It has been found that both the Pd^0 and Pd^{2+} species are effective in this reaction, since the Pd^{2+} can be reduced in the initial step. Thorand and Krause have suggested that a better choice of solvent is THF,[40] the reason being that it appears to aid in minimizing the amount of Glaser coupling (oxidative homocoupling of the alkyne) that will occur if oxygen is not

completely excluded from the reaction system. The reactivity of this coupling reaction is the same as the Stephen-Castro coupling with I>Br>Cl and the presence of electron-donating groups lower the activity while electron-withdrawing groups promote the reaction.

Scheme 14

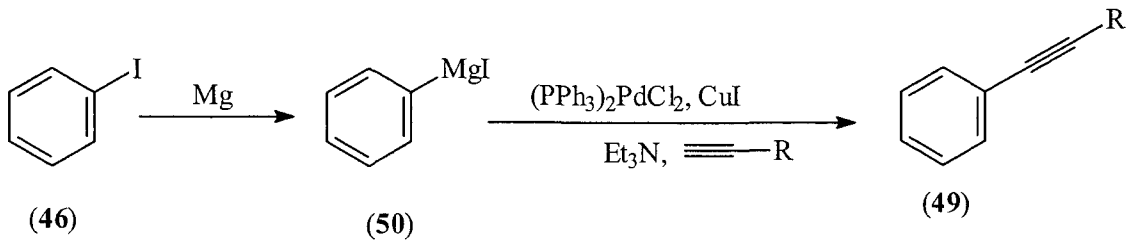


1.5.3 Grignard-Sonogashira Coupling

The coupling with an alkyne and aryl Grignard in place of an aryl halide has been performed which is a very recent improvement of the Sonogashira coupling reaction (Scheme **15**).[41] The yields are good to excellent even when electron-donating substituents are present. The most surprising consideration in this result is that the acidic nature of hydrogen attached to the *sp* hybridized carbon should interfere with Grignard reagents. Therefore, the expected result of the reaction would be a deprotonation of the alkyne with no coupling occurring. However, this deprotonation reaction only occurs to sparing degrees with the main product being that which would be expected from a standard Sonogashira coupling.

From this literature review, it can be seen that enediyne chemistry has become a useful tool in the synthesis of novel compounds;[42] however, the potential of enediynes has been overlooked in the synthesis of heteroaromatic systems.

Scheme 15

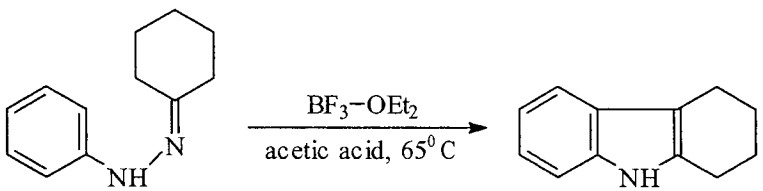


(46) **(50)** **(49)**

1.6 The Fisher Indole Synthesis

The most general synthesis of indoles is the Fisher indole synthesis, in which the phenylhydrazone of an aldehyde or ketone is treated with a catalyst such as BF_3, $ZnCl_2$, or polyphosphoric acid (PPA).[43] The result of this reaction is a substituted indole (**52**).

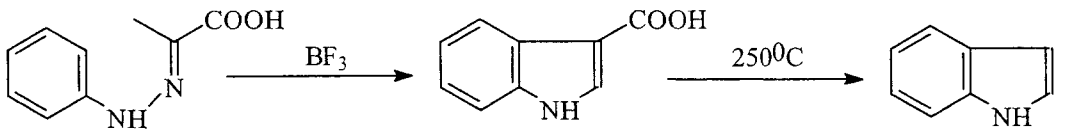
Scheme 16



(**51**) (**52**)

The preparation of an unsubstituted indole requires using the phenylhydrazone of pyruvic acid (**53**). The resulting indole (**54**) contains a carboxylic acid group, which undergoes decarboxylation to yield the unsubstituted product (**55**) (Scheme **17**).[43] The decarboxylation occurs only at 250°C, so the extreme reaction temperature makes this synthesis difficult to perform. It is hard to synthesize unsubstituted indole, so the determination of a simple method to do so is described. Since the structures of the three (thiophene, indole and furan) bicyclic heteroaromatic compounds differ only in the heteroatom it would be advantageous to develop a synthetic strategy using the same method to synthesize all three.

Scheme 17

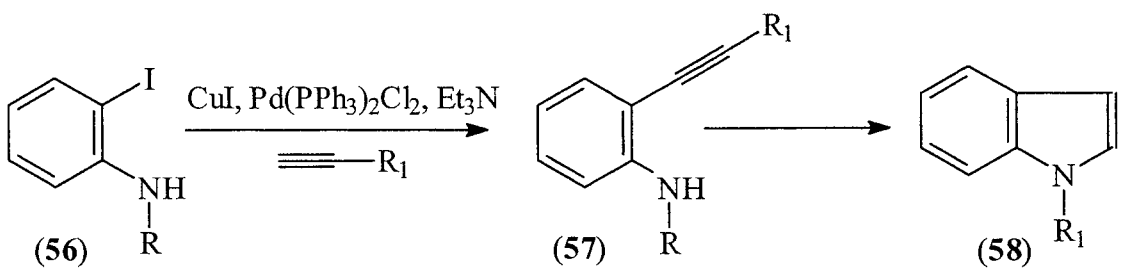


(53) (54) (55)

1.6.1 Modern Methods Of Benzothiophene, Benzofurans And Indole Synthesis

The synthesis of all three classes of compounds via coupling of an aromatic iodide derivative with alkynes catalysed by a Pd/CuI system has been reported.[44,45] A cross coupling reaction is carried out between ortho-substituted halobenzene, starting material (**56**), and the alkyne. The resulting product (**57**) can then spontaneously cyclize with the substituents in order to form the heterocyclic ring of the final product (**58**) (Scheme **18**).[44,45] The efficiency of the cyclization depends upon the nature of the R group, the base, and the reaction conditions.[44,45]

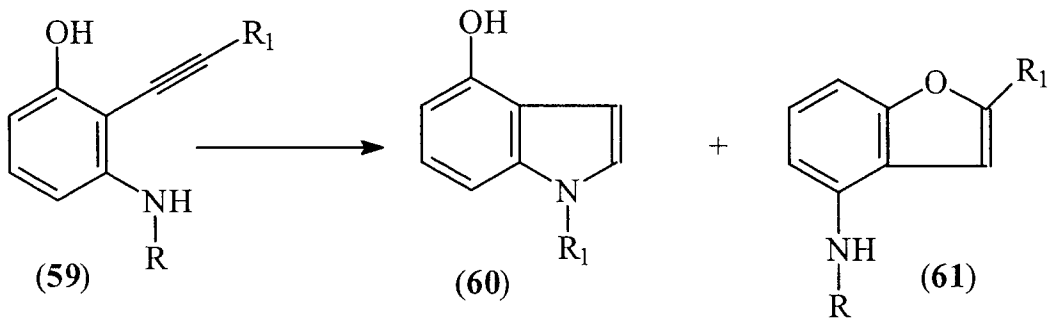
Scheme 18



(56) (57) (58)

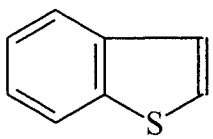
For the preparation of benzothiophene, the heteroatom substituent is thiol. Similarly, for benzofurans or indoles an hydroxyl or amine functionality would be required, respectively. By using this[44] and other methods,[45] very high yields (>99%) have been obtained, but this method has a major drawback. Once the product has been obtained (benzothiophene, indoles or benzofurans) substitution reactions cannot occur on the benzene nucleus, because the reactivity of carbons of heterocyclic ring is much greater. To obtain substitution on the benzo positions, it would have to be present in the initial starting material which can lead to problems. If substituents like amino or hydroxy groups are present in an additional site to which a cyclization can occur, then the cyclization may occur there rather that at the desired site (Scheme **19**). This would lead to the undesired products. It is these shortcomings that the work described herein is designed to overcome.

Scheme 19

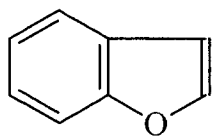


1.7 Benzothiophenes, Benzofurans And Indoles

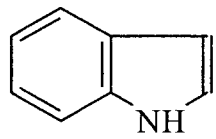
Benzothiophenes **62**, benzofurans **63** and indoles **64** are analogues of each other. All three consists of a six membered aromatic ring which is fused to a five-membered heteroatomic ring. The main difference between them is the nature of heteroatom, so all three compounds can generally be studied together and a common method of synthesizing all three compounds would be desirable.



(62)



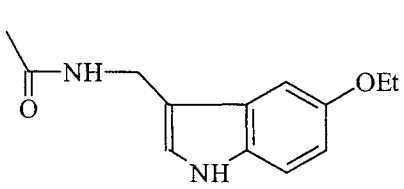
(63)



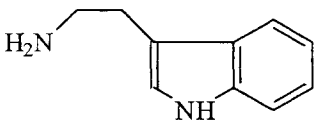
(64)

There are many naturally occurring, biologically active compounds that contain benzothiophene, benzofuran and indole cores. Melatonin (N-acetyl-5 methoxytryptamine) **65** is a simple example of an indole and one that is highly studied. Melatonin is an important antioxidant hormone produced especially at night in the pineal gland. Its secretion is stimulated by the dark and inhibited by light.[46] Tryptophan **66** is converted to serotonin[47] **67** and finally converted to melatonin. The suprachiasmatic nuclei (SCN) of the hypothalamus have melatonin receptors and melatonin may have a direct action on SCN to influence "circadian" rhythms. Melatonin is metabolised to 6-hydroxy-mel in the liver and the main metabolite excreted is 6-sulphatoxy-mel.[48] Isolated measurements of mel are difficult to interpret given its circadian secretion, however urinary excretion of 6-sulphatoxy-mel may be helpful in studying pineal function especially in children.

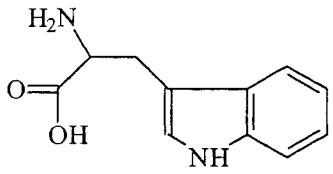
Raloxifene **68**, a naturally occurring benzothiophene derivative belongs to a class of drug called "selective (o)estrogen receptor modulators" or "SERMs".[49] It is able to attach itself to specific tissues in the body which are stimulated by oestrogen (female-type hormone) including bone. One of oestrogen's most important roles is to stimulate the production of new bone as part of the process by which the quality of the bones is maintained. Raloxifene, like oestrogen, can also stimulate target sites in bone tissue. When oestrogen levels fall (as they begin to after change of life) the bones become thin or brittle with the result that fractures are likely to occur. This is one of the common ways by which osteoporosis, which is associated with reduced bone density, occurs. Raloxifene is therefore used to maintain or increase bone density and thereby reduce the occurrence of fractures in post-menopausal women (or younger women without ovaries) who are at risk of osteoporosis or in whom osteoporosis is established. A further interesting effect of Raloxifene is that it also binds to oestrogen target sites on the breast but in this case it blocks stimulation of breast tissue by oestrogen[50] (a means by which many breast cancers develop). Raloxifene might therefore be considered as an alternative to HRT in osteoporosis if there are concerns about breast cancer due to a strong family history for the patient.



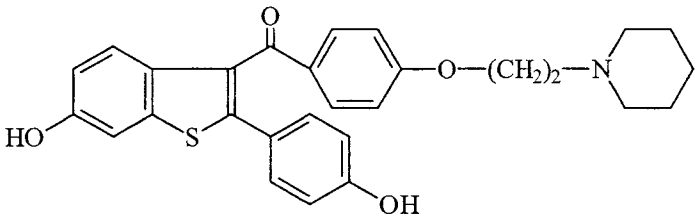
(65)



(66)



(67)



(68)

1.8 Synthesis And Applications Of Enediynes

Currently, new methods are being utilized in the design of enediynes, their synthesis, and their reactivity. The widespread approach uses a palladium coupling reaction between the alkyne and ene moieties.[51-53] Nuss *et al.* have been utilizing the Norrish type II cleavage of an α,β-unsaturated carbonyl to form the desired enediyne.[54] Grissom *et al.* have utilized tandem Bergman cyclization reactions to synthesize two- and three-fused-ring systems.[20,55] Finally, it has been found that by using the different metal ions, Cu(II), Zn(II) and Mg(II) with a Mg(II) complexed enediyne Bergman cyclization is promoted since the activation barrier to cyclization is lowered.[56,57]

Several factors must be considered for potential medical applications of enediyne analogues. The enediyne must have a planar component that can easily interact with DNA. The enediyne or its analogue must also be thermally stable at physiological conditions, and exhibit very low or no cytotoxicity. The activation of the analogue toward

the Bergman cyclization must have a specific, controllable trigger e.g. light. It should be synthetically simple. In this thesis, carbon-carbon cross coupling reactions and Bergman cyclization will be examined as a potential means of synthesizing substituted benzothiophenes. In Chapter Two, an outline for a novel approach to benzothiophene synthesis will be presented along with the preliminary steps taken in applying this methodology. This will be followed, in Chapter Three, by a series of competitive reactions of substituted aryl halides performed to determine their relative reactivities.

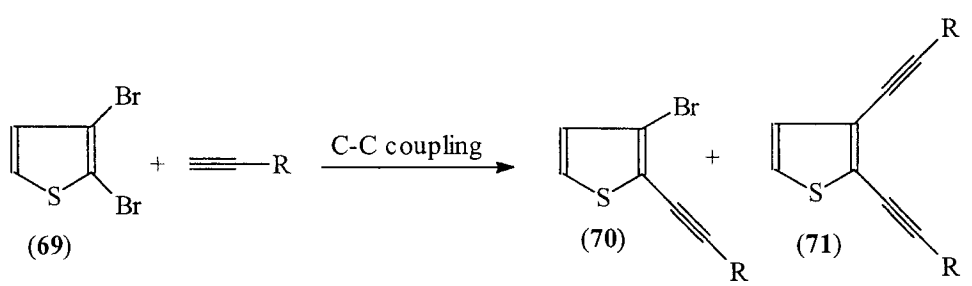
CHAPTER TWO

A STUDY OF SUBSTITUTED BENZOTHIOPHENE SYNTHESES

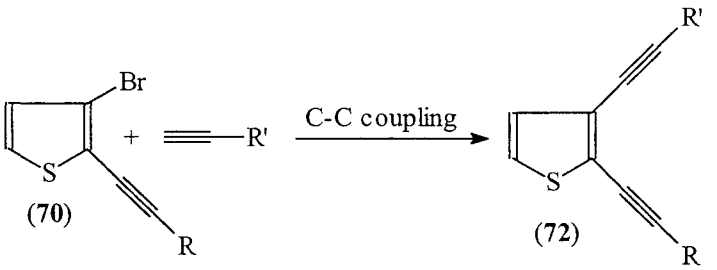
2.1 Introduction

In the preceding chapter, a review of enediyne chemistry was presented along with synthetic methods for the preparation of fused bicyclic heteroaromatic systems. In this chapter, an approach to the synthesis of substituted benzothiophenes is presented using a novel methodology. Enediynes may form an aromatic ring when they cyclize, so it may be possible to prepare benzothiophenes from thiophenes having substituents on the six-membered ring. This reaction scheme involves performance of a Sonogashira coupling reaction between an alkyne and 2,3-dibromothiophene (Scheme **20**). The reactivity at C-2 is much higher than that at C-3 because of the heteroatom. This results in a mixture of products **70** and **71**. Compound **70** can be isolated and subjected to another Sonogashira reaction (Scheme **21**). The ability to conduct each coupling reaction individually allows for a change of alkyne, thereby providing a means of introducing differing substituents into the system.

Scheme 20

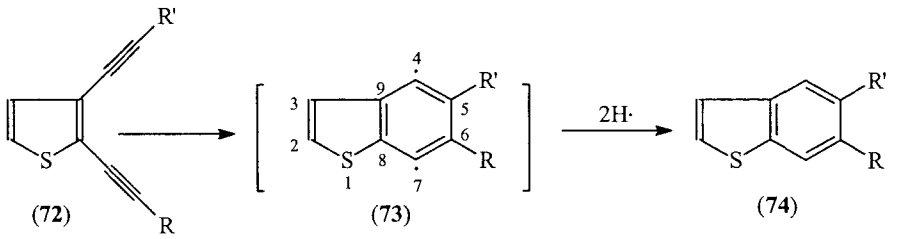


Scheme 21



After completion of the second coupling reaction to give **72,** the 1,5-diyne-3-ene functionality is formed. A Bergman cyclization can then be used to close the ring and form the substituted benzothiophene (Scheme **22**). The nature of substituents on the benzene portions of the ring system can be determined by the initial alkynes used in the cross couplings.

Scheme 22

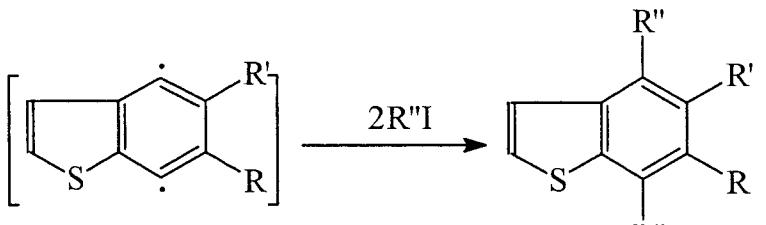


It has been mentioned in Chapter One that Bergman cyclization is known to proceed through both thermal and photochemical reaction pathways. This provides alternate methods to synthesize benzothiophenes.

The substituents on C-5and C-6 of the final product can be predicted by substituents on the alkyne terminal of the enediyne. It would be possible to introduce

substituents at the C-4 and C-7 positions through the biradical intermediate during the cyclization (Scheme 23). Substituents on the five-membered ring of the system can

Scheme 23



(73) (75)

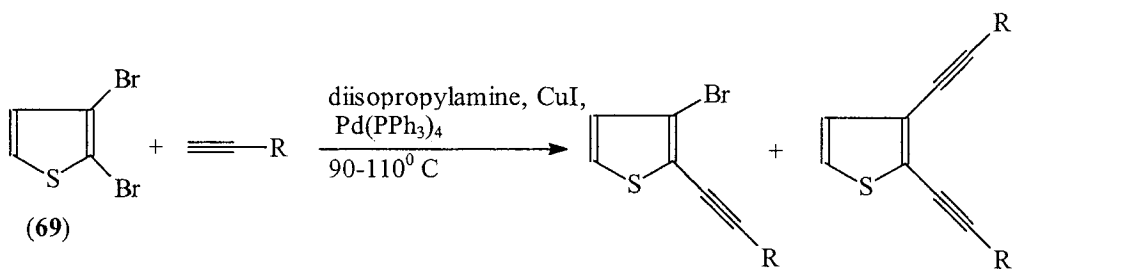
either be present on the initial 2,3-dibromothiophene or can be easily inserted using electrophilic aromatic substitution. It is believed that the same methodology can also be useful for indoles and benzofurans. This study focuses on benzothiophenes due to the commercial availability of the 2,3-dibromothiophene (**72**) starting material, and the time frame of the research project.

2.2 Synthetic Studies On Substituted Benzothiophenes

Commercially available 2,3-dibromothiophene is the starting material. This 2,3-dibromothiophene was coupled with a number of alkynes (Scheme **24**) by using the Sonogashira reaction. *Tetrakis*(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] is the catalyst, CuI is a co-catalyst and diisopropylamine is the solvent. Diisopropylamine was chosen to function as both the solvent and the base[26]. Reactions were completed in a sealed pressure tube and at 90-110°C for 13 hours under a nitrogenous atmosphere with stirring.[26] With standard conditions (at room temperature) it was found that no coupling

occurs at C-3 position. Therefore, higher temperatures were needed to prepare the disubstituted compounds.

Scheme 24



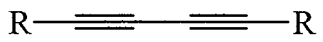
76: R = Ph
77: R = CH_2OH
78: R = $Si(CH_3)_3$
79: R = $C(CH_3)_2OH$

80: R = Ph
81: R = CH_2OH
82: R = $Si(CH_3)_3$
83: R = $C(CH_3)_2OH$

84: R = Ph
85: R = CH_2OH
86: R = $Si(CH_3)_3$
87: R = $C(CH_3)_2OH$

Our successful reactions utilizing this technique were done with 2,3-dibromothiophene and phenylacetylene, trimethylsilylacetylene and 2-methyl-3-butyn-2-ol resulting in **84**, **86**, **87** respectively. Compound **84** and **87** were separated from the reaction mixture and purified very easily and with good yields (86% and 88% respectively). Compound **86** and mono-coupled product **82** have almost similar polarities and retardation factor (R_f) in most solvents. **86** was isolated from the reaction mixture and purified by column chromatography in low yield (37%). However, propargyl alcohol (**77**) does not couple with 2,3-dibromothiophene under these conditions. The formation of **85** could not be confirmed by either GC-MS or TLC. It has also been found from GC-MS result that we did not get the compound **81** under these conditions. Furthermore, at low (70-85°C) and high (115-130°C) reaction temperature it was not possible to obtained either compound **81** or **85**. This result is most likely due to interference from the hydroxyl group during the coupling reaction. During the separation of enediyne compounds a number of byproducts

were found. These are most likely the dimer of alkynes (**88-91**), triphenylphosphine oxide ($O=PPh_3$) and mono-coupled products (**80-83**).



88: R = Ph
89: R = CH_2OH
90: R = $Si(CH_3)_3$
91: R = $C(CH_3)_2OH$

The dimer of alkynes (**88-91**) and mono-coupled products (**82-85**) were separated easily from the reaction mixture with column chromatography by using hexanes and ethyl acetate (95:5) in most cases. Triphenylphosphine oxide (($O=PPh_3$)) interfered with products and difficulties arose with the isolation of products. Column chromatography was run several times mostly using hexanes to purify the enediyne compounds from triphenylphosphine oxide ($O=PPh_3$).

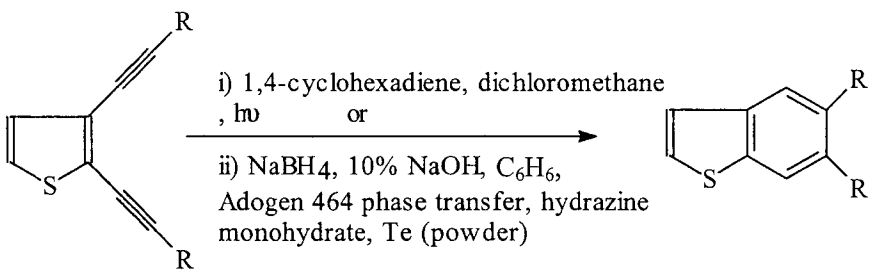
The general reactivity observed for the coupling reaction suggests that the polarity of the mono, di-coupled and starting materials impacted the isolated yields. The isolations of enediyne **84** and **87** were simple due to the high retention on silica relative to mono-coupled products. The tertiary hydroxyl group is sufficiently shielded by the two adjacent methyl groups; thereby it does not affect the coupling reactions and resulted in the higher yield of **87**. On the other hand, we propose the lack of success with propargyl alcohol is directly related to the primary hydroxy group. It is also may possible that the electron-withdrawing nature of this alkyne may have heightened the reactivity or the ability of

mono-coupled products (**83**) to hydrogen bond with another equivalent of alkyne and may have made the coupling of second alkyne more energetically favorable. The TMS di-coupled products were more difficult to isolate than the phenyl substituted products. It was observed that the retention factor for di-coupled Ph and di-coupled tertiary alcohol enediynes were very different from those of their corresponding mono-coupled products, which basically simplify the isolation and purifications as well.

2.3 Cyclization Of Enediynes

As has been mentioned previously, the Bergman cyclization reaction proceeds through both photochemical and thermal pathways. Therefore, both types of cyclization were attempted in order to generate substituted benzothiophenes from the enediynes that were successfully synthesized (Scheme **25**). An explicit hydrogen atom source such as 1,4-cyclohexadiene is not required for all the tellurium-mediated thermal cyclization reactions that were attempted.[58] For all photochemical cyclization reactions 1,4-cyclohexadiene was used as the hydrogen atom source.

Scheme 25



84: R = Ph
86: R = Si(CH3)3
87: R = C(CH3)2OH
92: R = H

93: R = Ph
94: R = Si(CH3)3
95: R = C(CH3)2OH
96: R = H

Compound **84** was the first synthesized product to be subjected to cyclization conditions. Unfortunately, this compound (**84**) shows a great stability under both sets of reaction conditions with no cyclized products nor other thermal degradation or photoreduction products being formed. This is most likely due to large *cd* resulting from the bulky Ph substituents, so the lack of cyclization is not surprising. However, a successful photochemical cyclization of an enediyne with Ph substituents (**31**) has been reported by Evenzahav *et al.*[34] It may be that the *cd* in **84** is slightly larger than **31** due to the five-membered ring having smaller internal angles. In addition, the heteroaromatic nature of this ring may alter the electronics enough that photochemical excitation does not occur. The difference in the outcome of these reactions might be determined by the relative phase of the molecular orbital lobes at the acetylenic carbon atoms in these systems. In **31**, the orbital lobes, at the two acetylenic carbon atoms, have the same phase in the HOMO of the tetraene and the HOMO, after excitation of the system, might have altered its phases. Two such acetylenic lobes can undergo photochemical cyclization. The presence of a heteroatom in **84** may prevent such a photochemical reaction. Furthermore, it is believed that a compound can only undergo photochemical cyclization with $(4n + 2)\pi$ systems.[59] This $(4n + 2)\pi$ is present in **31** while in **84** it is not.

Compound **87** was used for the next set of cyclizations. Again, no cyclized product was observed in either thermal or photochemical conditions. It shows a remarkable stability with no degradation products detected. This might due to the presence of tertiary alcohol groups, which would exert a great deal of steric interaction, forcing alkyne ends apart and preventing reaction. The same lack of reactivity under both

thermal and photochemical conditions was also observed for compound **86**. Under these conditions no degradation, polymerization or reduction products were detected from **86**.

Our group has previously worked with compound **92** (Scheme **25**) and it has been concluded that substituents are not preventing the cyclizations of enediynes.[60] Turro *at el.* report a solvent dependence for photochemical Bergman reactions where ethanol results in the highest yields of product.[34] It was also previously reported by our group that cyclization of heteroaromatic enediynes did not depend on solvent or photo sensitizer as well. As discussed earlier, it is believed that photochemical Bergman cyclization occurs from the singlet excited while photoreduction occurs from triplet state.[35]

The *cd* distances for the various enediynes were calculated theoretically at both the MOPAC and MM2 levels. The results are reported in Table 1.

Table 1: Theoretical Calculations of the *cd* Distance

Enediyne	MOPAC (Å)	MM2 (Å)
84	4.373	4.408
86	4.400	4.400
87	4.392	4.392
92	4.473	4.409

TMS-, phenyl and 3-methyl-3-hydroxy substituted enediynes had estimated *cd* between 4.473 - 4.373Å; all of the results fall outside of the critical ranges determined by

Nicolaou[21] and Schreiner[61] by approximately 1Å. It was unclear if their lack of reactivity was due to their larger *cd*, less reactive singlet state or a combination of these factors. The lack of reactivity may be a factor of the non-rigid acetylenic units, which would have to be overcome by adding a significant amount of heat energy, rendering it less reactive.

Turro *et al.* have reported successful photochemical cyclization of compounds **26** and **31**,[34] the *cd* distances again found to be outside of the critical range established by Nicolaou[21]and Schreiner.[61] (**26**:4.059Å by MOPAC and 4.051Å by MM2, **31**:4.082Å by MOPAC and 4.078Å by MM2) In Schreiner's study, it was found that the range is very precise given that some compounds, even though only slightly outside the range, do not cyclize. In Turro's results, it appears that the critical range is not as large a factor in the photochemical cyclization as in the thermal mechanism. However, the compounds we investigated here do not cyclize in either photochemical or thermal conditions.

2.4 Future Work

The Sonogashira coupling reaction can be applied very effectively to the synthesis of enediynes. Additional work has to be done in order to extend the range of enediynes that can be made. Thermal cyclization could be attempted at higher temperatures than have been reported here. Radical trapping agents can be used instead of 1,4-cyclohexadiene to investigate the reaction pathways. Further studies are required in order to improve cyclization and to expand the area of enediynes.

CHAPTER THREE

RELATIVE REACTIVITY OF SUBSTITUTED ARYL IODIDES IN THE SONOGASHIRA REACTION

3.1 Introduction

The inductive and resonance effects of substituents in the *meta-* and *para-* position of the benzene ring on the Sonogashira coupling reaction[37] were investigated by varying both the electron-withdrawing (EW) and electron-donating (ED) nature of the substituents. Earlier work[36] showed that electron-withdrawing groups increased the reactivity of coupling reaction while electron-donating groups decreased the reactivity according to the following order *p*-NO_2 > H > *p*-OCH_3 in the *para-* position. For this competitive reactivity study, a series of *meta-* and *para-* substituted iodobenzenes was selected. All of these substituted iodobenzenes varied from strongly electron-withdrawing to electron-donating and commercially available as well. A *para-* or *meta*-substituted iodobenzene was subjected to an intermolecular competition coupling reaction of an alkyne with iodobenzene in the presence of the co-catalyst system composed of Pd/CuI. At the end of reaction, the reaction mixture was run through the gas chromatogram (GC) in order to determine the relative reactivity of the substituents.

The reaction conditions for the Sonogashira competitive coupling reaction were chosen from the literature.[37] *Tetrakis*(triphenylphosphine)palladium (0) was used as a catalyst,

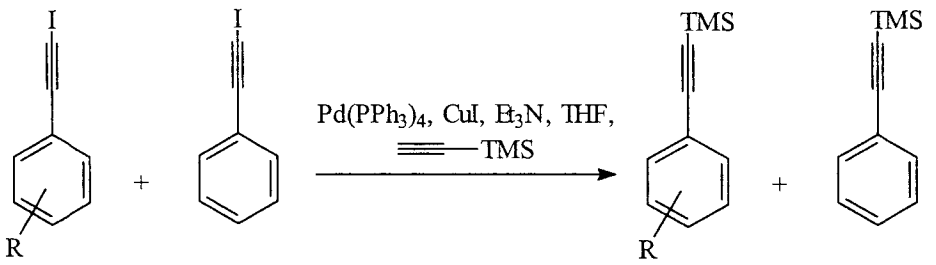
and cuprous iodide as a co-catalyst, as those have provided efficient couplings in the literature. TMS-acetylene has been chosen as the alkyne, and triethylamine was chosen as the base. In an attempt to optimize Sonogashira's coupling, variations in starting materials, and the order of addition of the alkyne and the catalyst were made.[40] High yields were observed when the reaction was completed in THF, equal or exceeding Sonogashira's yields after one hour.[40] It was also observed that the rate of the reaction increased when THF was used as the solvent, while the rate of Glasser coupling decreased, and when the alkyne was introduced with a slow, drop wise addition. All of these reactions were performed at room temperature. Initially, the intermolecular competition was carried out using 1 equivalent (1 mmol) each of iodobenzene and the substituted iodobenzene in the presence of 0.5 equivalents (0.5 mmol) of TMS-acetylene, 2 mol % Pd (0.20 mmol) and 6 mol % CuI (0.06).

A series of experiments was run to obtain pure alkynyl products for each of the compounds studied. This pure product was analyzed via GC using a known amount of alkyne and biphenyl to obtain an R_f value for each. When the kinetic experiments were performed a measured amount of biphenyl was added to the GC mixture and the yield of each alkyne (substituted and unsubstituted) was calculated using the previously measured R_f. Then the relative rates of reactivity were calculated as well.

The use of such a large amount of TMS-acetylene did not support the kinetic relationship developed and the competition reactions were performed again with 0.05

equivalents of alkyne. All of the other reaction conditions were the same as before. The general reaction equation is shown in Scheme **26**.

Scheme 26



R = OH, CH_3, CN, NO_2, CF_3, OCH_3, C_2H_5, NH_2

97: R = *m*-OH
98: R = *p*-OH
99: R = *m*-CH_3
100: R = *p*-CH_3
101: R = *m*-CN
102: R = *p*-CN
103: R = *m*-NO_2
104: R = *p*-NO_2
105: R = *m*-CF_3
106: R = *p*-CF_3
107: R = *m*-OCH_3
108: R = *p*-OCH_3
109: R = *m*-C_2H_5
110: R = *p*-C_2H_5
111: R = *m*-NH_2
112: R = *p*-NH_2

We have calculated the rate constants from competitive reactions between iodobenzene and a number of *meta-* and *para-* substituted iodobenzene in the Sonogashira reaction. These results were compared with the theoretical electron densities of iodide bearing carbon and were also used to assume the type of intermediate in the rate determining step by established linear correlations. Our data and plots support the previous observations.[36] (see Appendix for full details)

3.2 Relative Reactivities For The Competitive Coupling Study

A series of intermolecular competitive reactions were performed to establish relative reactivities due to changing the electronic nature of substituents, as described above. We correlated the relative rate constants with Hammett substituents constants (σ,

σ^+, σ^-). The relative rate constants for Sonogashira coupling reactions (using 0.5 equivalent of TMS-acetylene) are tabulated in Table 2.

Table 2: Relative Rate Constants Of Sonogashira Coupling Reaction With 0.50 Equivalents TMS-Acetylene

Entry	R	$k_{relative}$
1	*m*-NO_2	0.68
2	*m*-CF_3	0.88
3	*m*-Me	1.40
4	*m*-OMe	0.43
5	*m*-OH	5.29
6	*m*-NH_2	0.67
7	*p*-NO_2	0.76
8	*p*-CF_3	1.03
9	*p*-Et	1.63
10	*p*-Me	0.98
11	*p*-OMe	1.49
12	*p*-OH	5.08
13	*p*-NH_2	0.31

Table 3: Electron Density of Iodide-Bearing Carbon*

3 (R=)	Electron Density	4 (R=)	Electron Density
m-OMe	-0.090	*p*-OMe	-0.017
m-NO_2	-0.179	*p*-NO_2	-0.099
m-CF_3	-0.155	*p*-CF_3	-0.115
m-Me	-0.123	*p*-Me	-0.135
m-OH	-0.087	*p*-OH	-0.172
m-NH_2	-0.065	*p*-NH_2	-0.188
H	-0.129	-	-

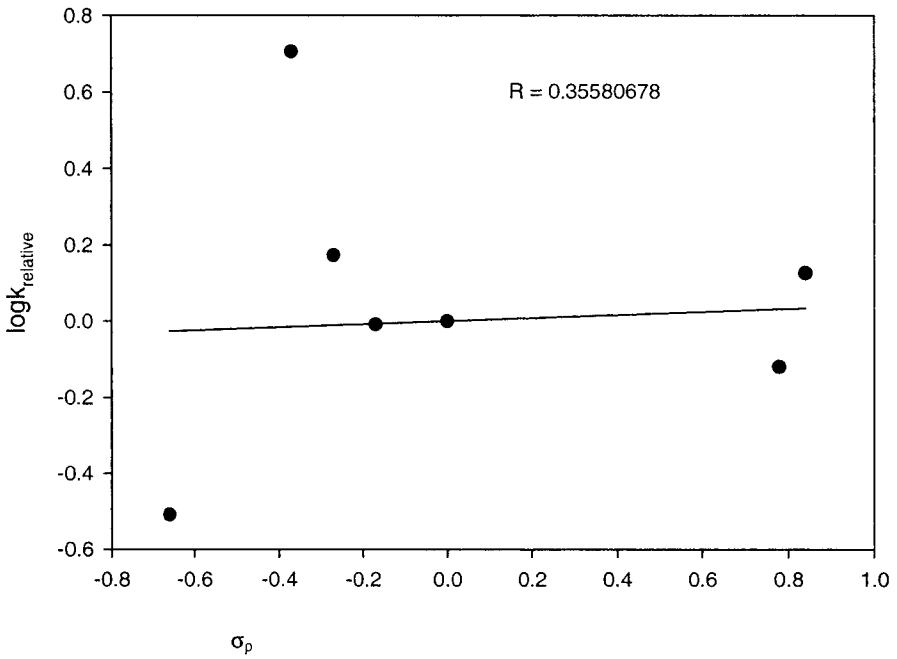
**Calculations performed using MOPAC 2002 Version 1.33 CAChe, PM3 Hamiltonian used.*

The $k_{relative}$ results (Table 2) and electron densities (Table 3) do not exhibit the same trends. From $k_{relative}$ we can determine the order of reactivity from most reactive to least reactive as: *m*-OH > *p*-OH > *p*-Et > *p*-OMe > *m*-Me > *p*-CF_3 > *p*-Me > *m*-CF_3 > *p*-NO_2 > *m*-NO_2 > *m*-NH_2 > *m*-OMe > *p*-NH_2. Calculations show the following trend in electron density at the iodide bearing carbon from lowest electron density to highest electron density: *m*-NH_2< *m*-OH < *m*-OMe < *p*-NO_2 < *p*-CF_3 < *m*-Me < H < *p*-Me < *m*-CF_3 < *p*-OMe < *p* –OH < *m*-NO_2 < *p*-NH_2. This result was unexpected and might be due to various reasons. For the hydroxy substituent, this is due to the inductively withdrawing nature in the *meta*-position, since that makes it more reactive than iodobenzene. The acidity of the hydroxyl proton might also affect reactivity, possibly through interference

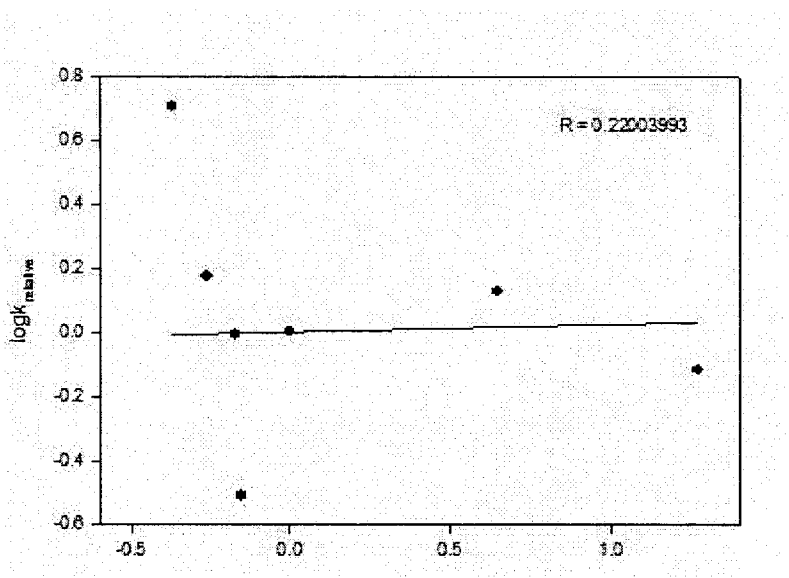
with catalyst or base. The reactivity of *para*-ethylbenzene was also unexpected. The electron donating nature of ethyl substituent should have made it less reactive than iodobenzene; however, the opposite effect was observed. This indicated that the weakly electron-donating ethyl substituent was different from the iodobenzene. The same effect was also observed for *m*-iodotoluene. The effect of methyl substituent was not very different from iodobenzene. The *para*-iodoanisole reacts faster than iodobenzene. This reactivity was attributed to the inductively electron-withdrawing nature of the substituent which should be less important than the electron donation by resonance. The methoxy substituent is an electron-withdrawing group by induction but not by resonance and showed a greater reactivity than iodobenzene was not expected. The electron-withdrawing *m*-iodo-α,α,α-trifluorotoluene shows unexpected reactivity. The CF_3 group is supposed to affect the electronic nature and accelerate the reaction but we did not observe this. The strongly electron-withdrawing NO_2 group in iodobenzene also shows unexpected reactivity; again the relative rate of reaction should have increased.

We tried to fit these observations to a linear relationship.[62] Plotting $logk_{relative}$ against substituent constant, σ, gives three graphs (Graph 1, 2 & 3). None of these graphs shows linear relationship and their linear regression value was unexpected. We then tried to fit the linear relationship between $logk_{relative}$ and substituent constant σ without hydroxy group but the relationship did not improve.

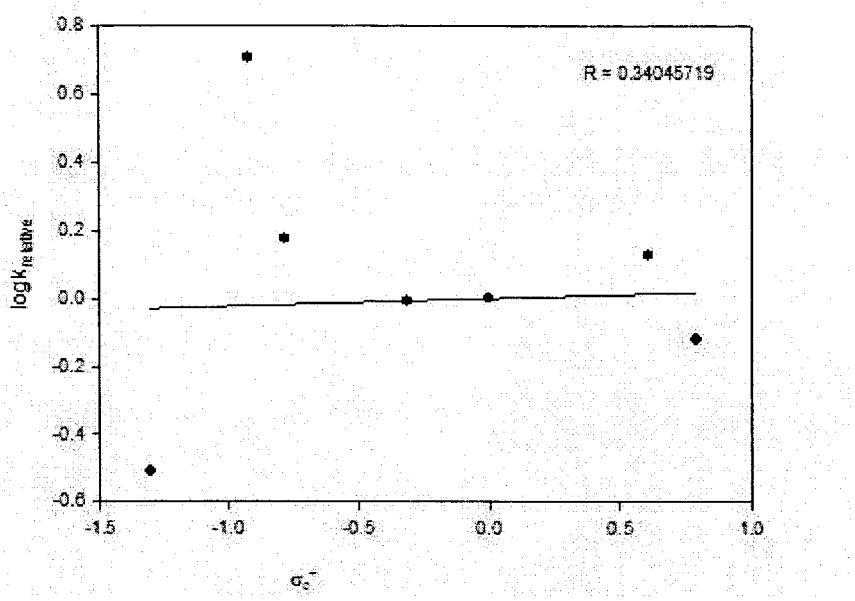
Graph 1: Plot of *logk*$_{relative}$ against σ_p for competitive rate reaction between iodobenzene and substituted iodobenzene:



Graph 2: Plot of *logk*$_{relative}$ Against σ_p^+ for Competitive Rate Reaction Between Iodobenzene And Substituted Iodobenzene



Graph 3: Plot of $logk_{relative}$ Against σ_p^- For Competitive Rate Reaction Between Iodobenzene And Substituted Iodobenzene



Next we proceeded with the intermolecular competition reaction which was carried out by the same procedure only with 0.05 equivalent of TMS-acetylene. The kinetic relationship developed upon a constant [S]/[US] ratio and with 0.5 equivalent of TMS-acetylene it is not reasonable to assume that this ratio is maintained over the course of the reaction. To ensure accuracy the reaction mixture was analyzed at least two times for each experiment. The experimental results (relative rate constants, $k_{relative}$) are tabulated in **Table 4**.

Table 4: Relative Rate Constants Of Sonogashira Coupling With 0.05 Equivalent TMS-Acetylene

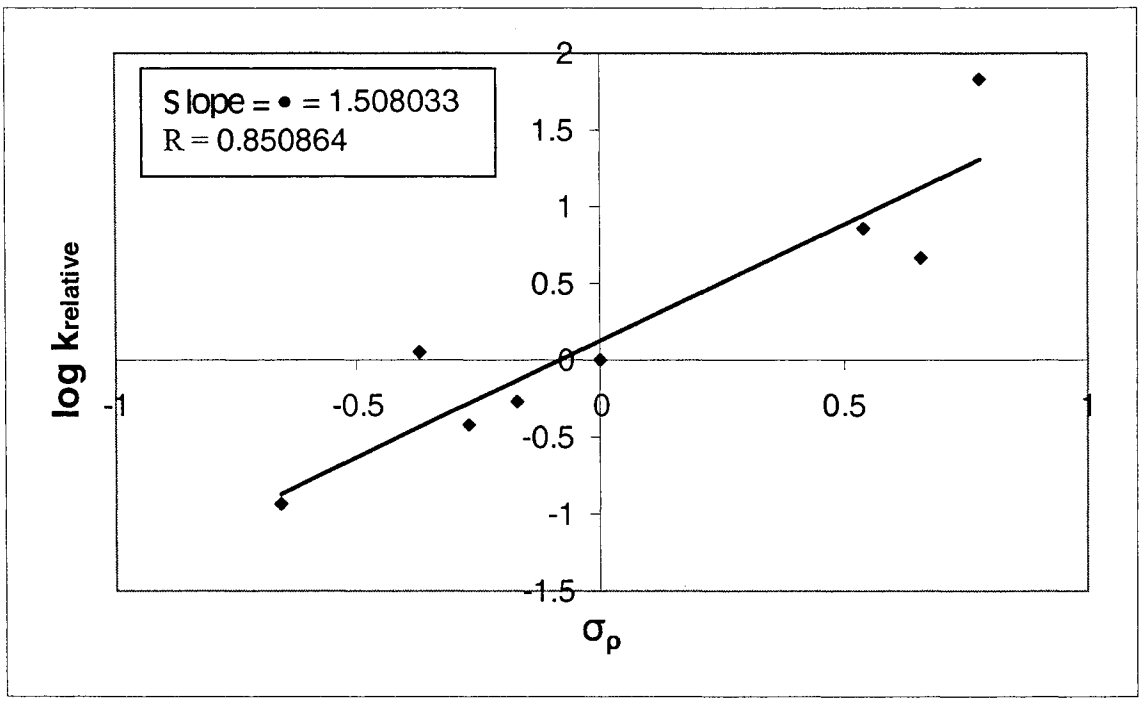
Substituents	$k_{relative}$	Substituents	$k_{relative}$
m-NO_2	4.2	*p*-NO_2	67.7
m-CF_3	5.0	*p*-CF_3	7.2
m-CN	2.9	*p*-CN	4.7
m-OH	0.3	*p*-OH	1.1
m-CH_3	1.4	*p*-CH_3	0.5
m-OCH_3	1.0	*p*-OCH_3	0.37
		p-Et	0.36
m-NH_2	0.3	*p*-NH_2	0.1

From $k_{relative}$ (Table 4) we can determine the order of reactivity from most reactive to least reactive as: *p*-NO_2 > *p*-CF_3 > *m*-CF_3 > *p*-CN > *m*-NO_2 > *m*-CN > *m*-CH_3 > *p*-OH > *m*-OCH_3 > *p*-CH_3 > *p*-OCH_3 > *p*-Et > *m*-OH > *m*-NH_2 > *p*-NH_2. The high reactivity of nitrobenzene and the *p*-iodo-α,α,α-trifluorotoluene were expected due to strong electron-withdrawing nature of their substituents in a resonant (*para*) position. The greater reactivity of CN was also found which was also expected. Besides this, the electron-donating substituents compounds exhibited the reverse reactivity. A large decrease in relative reactivity was observed with the reaction of iodoaniline. It showed that it is less reactive than iodophenol and iodoanisole. This reactivity trend was expected as NH_2

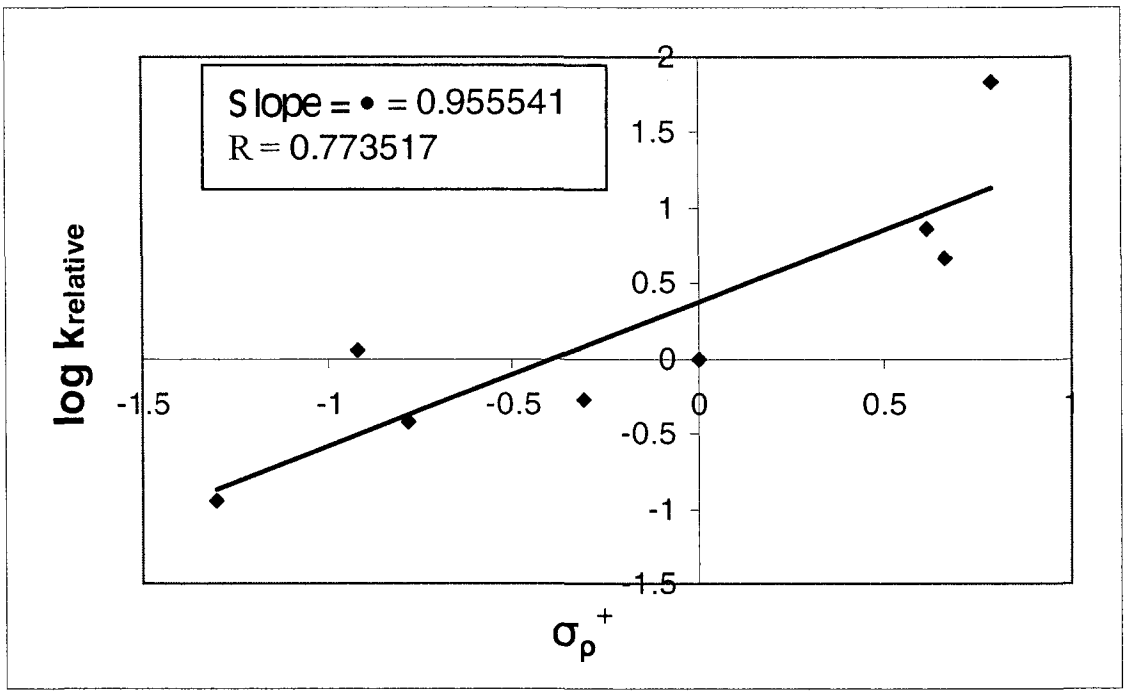
substituent is less electron withdrawing than both OH and OCH_3 substituents. It could be explained that with two lone pairs of electrons on the oxygen atoms in OH and OCH_3, and the increased electronegativity of O with respect to N, the substituents decrease the π-donation into the ring relative to aniline. The alkyl substituted iodobenzenes were more reactive due to their weaker electron donating nature. The calculated value indicated that *p*-ethyliodobenzene was less reactive than *p*-iodotoluene.

Three graphs are obtained by plotting of $logk_{relative}$ against substituent constant σ. It is worth mentioning that although most of the relative reactivity was expected the graphs do not have a linear regression values (R) closer to 1.

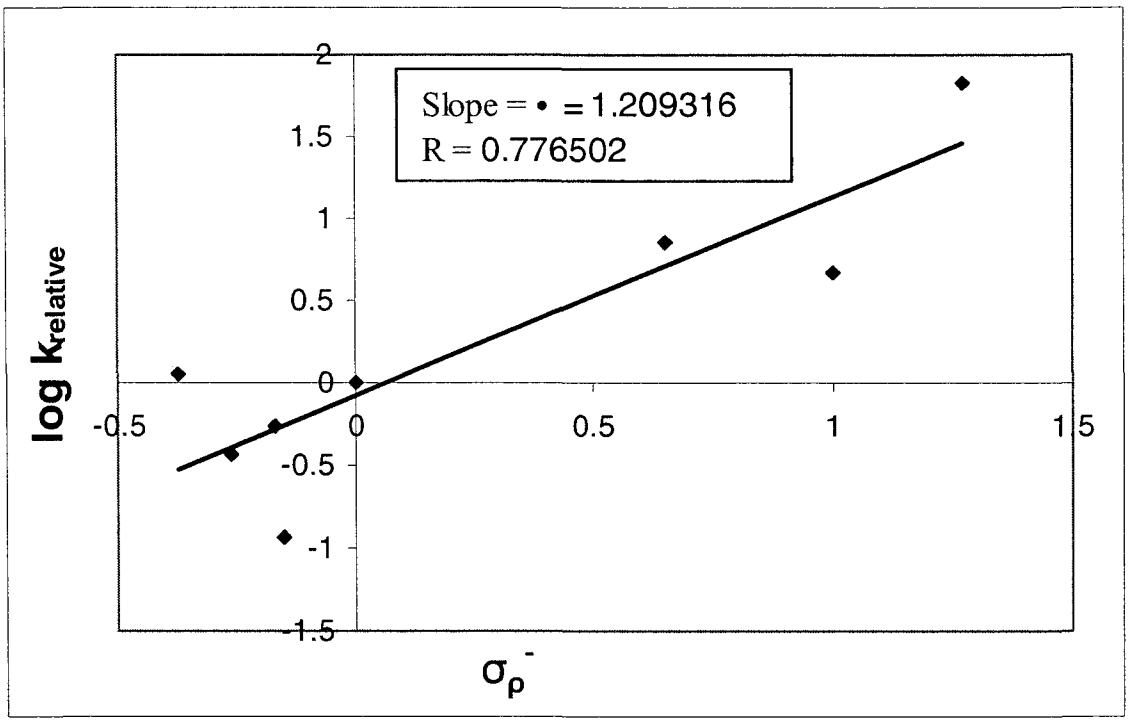
Graph 4: Plot of $logk_{relative}$ Against σ_p For Competitive Rate Reaction Between Iodobenzene And Substituted Iodobenzene



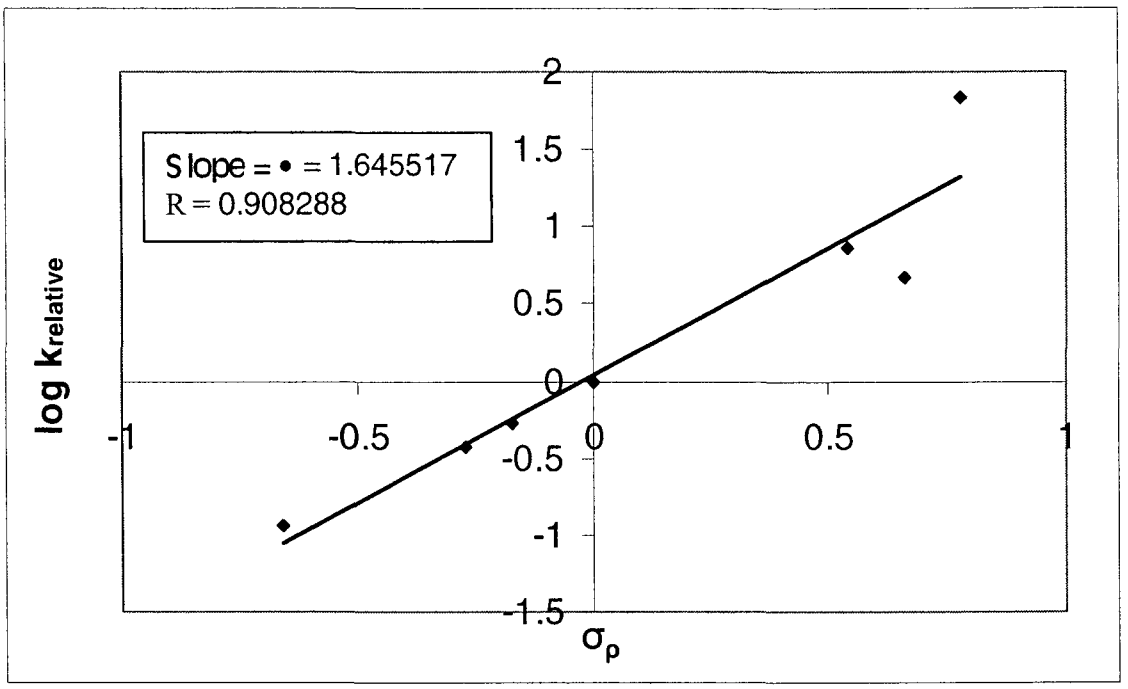
Graph 5: Plot of $logk_{relative}$ Against σ_p^+ For Competitive Rate Reaction Between Iodobenzene And Substituted Iodobenzene



Graph 6: Plot Of $logk_{relative}$ Against σ_p^- For Competitive Rate Reaction Between Iodobenzene And Substituted Iodobenzene



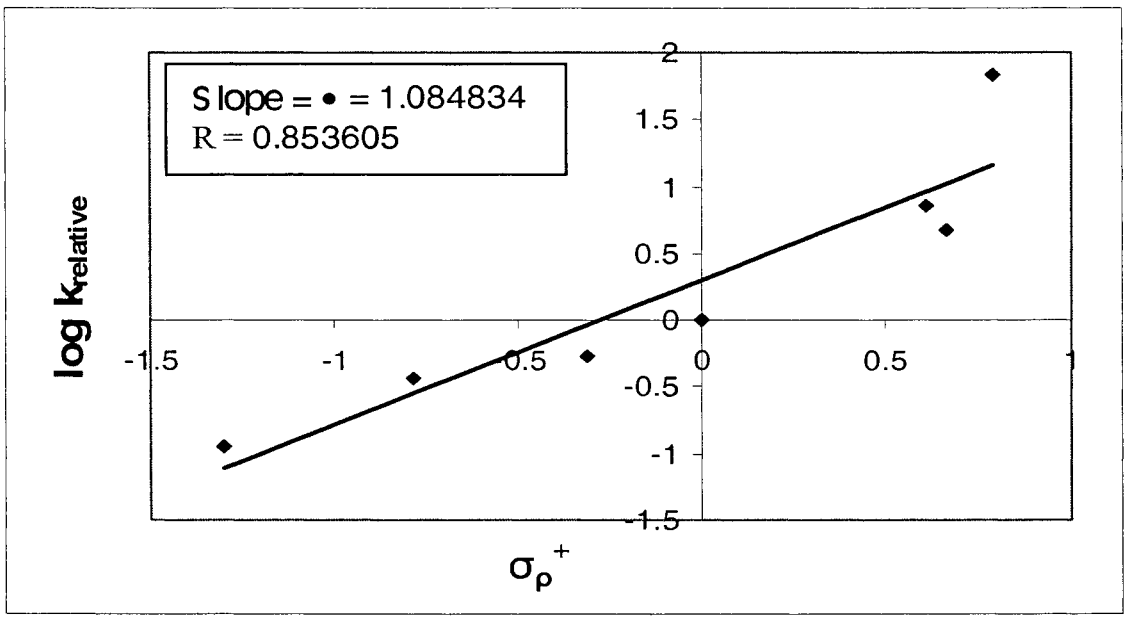
Graph 7: Plot of $logk_{relative}$ Against σ_p For Competitive Rate Reaction Between Iodobenzene And Substituted Iodobenzene (OH Exclude)



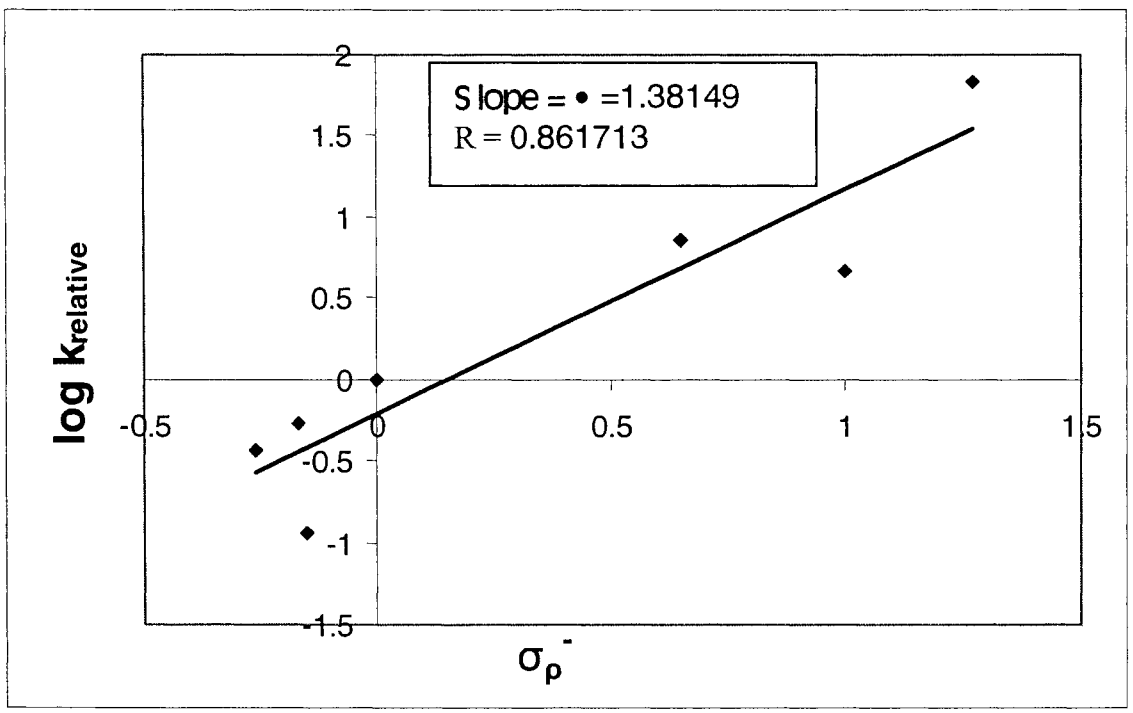
It is very interesting that although these graphs did not fit linearly with the exclusion of only the OH a straight line with reasonable R values was obtained. By excluding OH (Graph **7** and Graph **8** and Graph **9**) were obtained.

The behaviour of the hydroxyl substituent does not fit the standard Hammett relationship. Perhaps the acidity of hydroxyl proton affects reactivity through interference with catalyst or base. It might also interfere through H-bonding with catalyst or base. Among the three plots (Graph **7**, **8** and **9**) Graph **7** gives a line with good regression. In Graph **7**, the two most powerfully electron-withdrawing substituents NO_2 and CF_3 lie away from the straight line, indicating that *p*-iodonitrobenzene and *p*-iodo-α,α,α-trifluorotoluene poorly correlate with others.

Graph 8: Plot of $logk_{relative}$ Against σ_ρ^+ For Competitive Rate Reaction Between Iodobenzene And Substituted Iodobenzene (OH Exclude)



Graph 9: Plot Of $logk_{relative}$ Against σ_ρ^- For Competitive Rate Reaction Between Iodobenzene And Substituted Iodobenzene

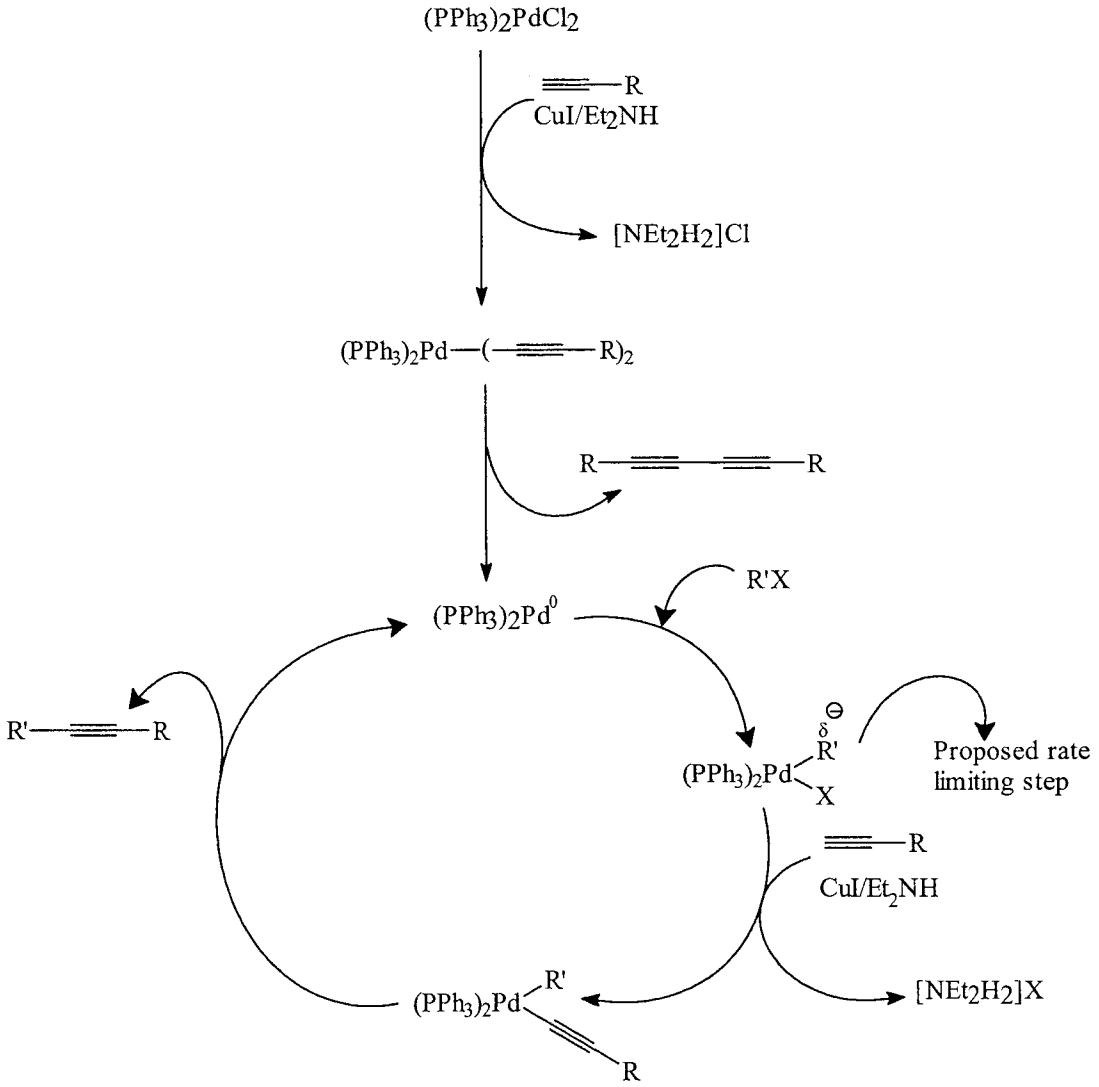


The inductive effect of the *p*-NO_2 substituent which will be essentially similar in each of resonant species, has been omitted, but the mesomeric and conjugative effects have been included. The conjugative effect of the *m*-NO_2 substituent is transmitted ultimately to the reaction centre only through an inductive effect. However, the conjugative effect can be transmitted directly from the *p*-NO_2 substituent to the reaction centre where the transition state ion will be stabilized substantially by delocalization of its charge and thus increasing the reactivity. The ability to stabilize the change in electron density at the reaction centre by an atom attached directly to the benzene ring in such reactions during the rate limiting step will be obviously differ from one compound to another.

The positive value of the slope, ρ (Graph **7**) suggests that the development of substantial negative charge in the transition state or the rate-limiting step. The value of slope (for Graph **7,** slope is 1.38) is greater than 1 which indicates that at the reaction centre electron density is increased in the transition state. If $|\rho| > 1$ that means reaction centre is more sensitive to the substitution than benzoic acid (for benzoic acid $\rho = 1$ at 25^0C) and, therefore, the rate-limiting step involves an increase in electron density at the reaction centre. Based on the proposed Sonogashira mechanism, the rate limiting step might be on the oxidative addition to the palladium catalyst (Scheme **27**). This addition results in the development of negative charge at the reaction centre; the palladium is directly attached to the substituted benzene ring in the forming intermediate (rate-limiting step). The reaction is thus accelerated by the electron-withdrawing substituents. So this can be regarded as a measure of the susceptibility of a reaction to the electron-donating or electron-withdrawing effect exerted by a substituent; where that for *m*- and *p*-substituted benzoic acids at 25^0C is $\rho = +1$. The higher magnitude of the ρ can be regarded as a

measure of the change in charge density at the reaction centre during formation of the transition state or on proceeding from one side of the equilibrium to the other. The development of charge in the transition state goes hand-in-hand with bond breaking between the reaction centre and the leaving group, our proposed rate-limiting step can perhaps be constructed as some indication of the extent of such reactions.

Scheme 27



3.3 Conclusion

The relative reactivity study correlated with previously established data and hypothesis.[36] It could be concluded that substituents that were in a *para*-position to an aryl halide exerted a significant resonance and mesomeric effect that governed the reactivity. The overall reactivity trend was very similar to the σ_m and σ_p values for the substituents except OH. The trend of reactivity in *meta*-position was not always obvious. Strong electron-withdrawing substituents increased reactivity through induction. Electron-donating substituents are expected to decrease the reactivity. A less pronounced effect occurred when the substituents was not in a resonant position where weaker inductive forces played a role.

CHAPTER FOUR

EXPERIMENTAL

4.1 General Experimental Techniques, Instrumentation, and Materials

All experiments were performed in flame-dried flasks under positive pressure of N_2 unless otherwise stated in the procedure. Coupling reactions were performed in 15 mL Ace pressure tubes, flame-dried under N_2. Thermal cyclizations were performed in 38 mL Ace pressure tubes which had been flame-dried under N_2. Photochemical cyclizations were performed in quartz tubes flame-dried under N_2 and irradiated with a Hanovia 200 W medium pressure Hg arc lamp at 25 ± 1°C. Liquid, moisture and air sensitive reagents were introduced to reaction mixtures through rubber septa using a syringe. All reactions were completed under inert an atmosphere of nitrogen or argon, and all yields reported are isolated yields unless otherwise stated.

Solvents used for experiments were subjected to drying prior to use. Specifically, tetrahydrofuran (THF) was distilled from potassium, dichloromethane (CH_2Cl_2) was dried over molecular sieves for six hours, triethylamine (Et_3N) and diisopropylamine ($^iPr_2NH$) were dried over calcium hydride and distilled over P_2O_5. Reaction progress was monitored using analytical thin layer chromatography (TLC) and gas chromatography (GC).

TLC was performed on silica gel of 2-17 μm particle size, 60 Å pore size and a thickness pf 250 μm with a 254 nm fluorescence indicator. The solvents used are reported in parentheses and the concentrations were in molarities at 25^0C. Visualization of spots was achieved by viewing under UV light. GLC was performed on Hewlett Packard 5890 equipped with flame ionization detector (FID) using a 30 m by 0.25 nm DB-5HT column composed of (%5 phenyl) methylpolysiloxane. The carrier gas was nitrogen or helium with a flow rate of 2.0 mL/min and a column head pressure of 21 psi. The temperature program used was the following: initial temperature =80˚C, initial time = 5 minutes, rate 10˚C/minute, final temperature = 280˚C, final time 10 minutes. Gas chromatography-mass spectrometry (GC-MS) was used to identify the mass of GC peaks.

Excess solvents were removed *in vacuo* on a Buchi rotary evaporator at pressure obtained by water aspirator. All crude samples and purified compounds were stored in the freezer under nitrogen at -10˚C. Reaction mixtures were purified by liquid chromatography. Separation was attained using 70-230 mesh silica gel. The solvent system used for separation was determined by analytical TLC.

Proton nuclear magnetic resonance (^{1}HNMR) spectra were obtained on a Varian AS500 using the ^{UNITY}INOVA NMR spectrometer system, VNMR 6.1C software and a switchable PF6 NMR probe at room temperature (unless otherwise stated). Deuterated chloroform ($CDCl_3$) was the solvent used with an internal standard of 1% tetramethylsilane (TMS). Chemical shift values are reported in parts per million (ppm) in the form: chemical shift (multiplicity, coupling constant in Hz, integration). ^{13}C NMR

spectra were obtained on the same instrument, using the same solvent. $CDCl_3$ (δ 77.0) was used as the internal standard, with values reported in ppm downfield from TMS.

Infrared (IR) spectra were measured on either a Perkin Elmer 1320 IR spectrometer or a Bruker IFS-66 Fourier transform infrared (FTIR) spectrometer with a resolution of 4 cm^{-1}. All spectra were determined neat unless otherwise noted, in the transmission mode using KBr plates and are reported as wavenumbers. Ultraviolet spectra were measured using a Perkin-Elmer Lambda 11 spectrometer, in ether or dichloromethane (CH_2Cl_2) using a quartz cuvet, and are reported as wavelength of maximum absorption (in nm) with the corresponding molar absorptivity (ϵ).

Tetrakis(triphenylphosphine)palladium(0)[63] was synthesized using previously described methods. All other chemicals for which procedures are not listed were purchased from Aldrich.

4.2 Preparations

Experimental For Chapter Two

1,2-(diphenylethynyl)thiophene **84**

2,3-Dibromothiophene (0.112 mL, 241mg, 1.0 mmol) *tetrakis*(triphenylphosphine)palladium(0) (24 mg, 0.02 mmol), and CuI (24 mg, 0.02 mmol) were combined in diisopropylamine (4.0 mL) in a dry pressure tube. The system was degassed with argon for 4-5 minutes. Phenylacetylene (0.275 mL, 256 mg, 2.5 mmol) was added. The tube was sealed and allowed to stir in an oil bath at 90-110^{0}C for

13 hours. The mixture was filtered through Celite with diethyl ether. Excess solvent was removed *in vacuo* and the product purified by column chromatography (hexanes: ethylacetate = 95:5) to give 245 mg (86%) of **84** as a brown solid.

TLC (hexanes: ethylacetate = 95:5): R_f: 0.15.

UV(CH_2Cl_2): λ_{max} = 277(ϵ = 0.5)

IR(neat): 3111, 3081, 3060, 2925, 2201, 1600, 1490, 1445, 1070, 1027, 755, 690.

^{1}HNMR($CDCl_3$): δ 7.55-7.34(m, 10H, Ph), 7.22(d, J = 5.0 Hz, 1H,H-4), 7.10(d, J = 5.0 Hz, 1H, H-5).

^{13}CNMR($CDCl_3$): δ 130.4, 128.4, 127.4, 125.2, 122.1, 121.8, 96.6, 92.6, 83.0, 81.0.

MS: (284 (100), 239(13), 142(7), exact mass calcd for $C_{20}H_{12}S$ *m/z* 284.066, obsd *m/z* 284.079.

bis-2,3-(3-hydroxyl-1-propanyl)thiophene **85**

2,3-Dibromothiophene (0.112 mL, 241mg, 1.0 mmol) *tetrakis*(triphenylphosphine)palladium(0) (24 mg, 0.02 mmol), and CuI (24 mg, 0.02 mmol) were combined in diisopropylamine (4.0 mL) in a dry pressure tube. The system was degassed with argon for 4-5 minutes. Propargyl alcohol (0.145 mL, 2.5 mmol) was added. The tube was sealed and allowed to stir in an oil bath at 90-110^{0}C for 13 hours. The mixture was filtered through Celite with diethyl ether. No product (by GC-MS) was obtained.

1,2-*bis*-(trimethylsilylethynyl)thiophene **86**

2,3-Dibromothiophene (0.112 mL, 241mg, 1.0 mmol) *tetrakis*(triphenylphosphine)palladium(0) (24 mg, 0.02 mmol), and CuI (24 mg, 0.02 mmol) were combined in diisopropylamine (4.0 mL) in a dry pressure tube. The system was degassed with argon for 4-5 minutes. Trimethylsilylacetylene (0.353 mL, 245 mg, 2.5 mmol) was added. The tube was sealed and allowed to stir in an oil bath at 90-110^{0}C for 13 hours. The mixture was filtered through Celite with diethyl ether. Excess solvent was removed *in vacuo* and the product purified by column chromatography (hexane : ethylacetate = 95:5) to give 245 mg (86%) of **86** as a dark liquid.

TLC (hexanes: ethylacetate = 95:5): R_f: 0.15.

UV(CH_2Cl_2): λ_{max} = 293(ϵ = 0.6)

IR(neat): 2984, 2100, 1292, 1184, 1101, 949, 835, 775.

^{1}HNMR($CDCl_3$): δ 7.09(d, J= 5.0 Hz, 1H, H-4), 6.97(d, J = 5.0 Hz, 1H, H-5), 0.27(s, 9H, $Si(CH_3)_3$),

0.26(s, 9H, $Si(CH_3)_3$).

^{13}CNMR($CDCl_3$): δ 129.46, 127.63, 127.27, 125.95, 103.62, 98.94, 98.78, 96.36, 0.101.

^{29}SiNMR($CDCl_3$): δ (-)16.89, (-) 17.30

MS: 276(77), 200(10), 172(12), 122(17),73(158), exact mass calcd $C_{14}H_{20}SSi_2$ *m/z* 276.544, obsd *m/z* 276.077.

2,3-bis-(3-hydroxy-3-methylbut-3-ynyl)thiophene **87**

2,3-dibromothiophene (0.112 mL, 241 mg, 1.0 mmol) tetrakis(triphenylphosphine)palladium(0) (24 mg, 0.02 mmol), CuI (24 mg, 0.02 mmol)

were combined in diisopropylamine (4.0 mL) in a dry pressure tube. The system was degassed with argon for 4-5 minutes. 2-Methyl-3-butyn-2-ol(0.242 mL, 210 mg, 2.5 mmol) was added. The tube was sealed and allowed to stir in an oil bath at 90-110^{0}C for 13 hours. The mixture was filtered through Celite with diethyl ether. Excess solvent was removed *in vacuo* and the product purified by column chromatography (hexane : ethylacetate = 95:5) to give 245 mg (86%) of **87** as a brown solid powder.

TLC (hexanes: ethylacetate = 95:5): R_f: 0.15.

UV(CH_2Cl_2): λ_{max} = 284(ϵ = 1.3)

IR(neat): 3333, 2963, 2924, 1423, 1421, 978, 918, 704.

^{1}HNMR($CDCl_3$): δ 7.13(d, J = 5.0 Hz, 1H, H-4), 6.94(d, J = 5.0 Hz, 1H, H-5), 1.63-1.58(m,12H, CH_3).

^{13}CNMR($CDCl_3$): δ 129.17, 126.70, 125.89, 101.90, 98.07, 76.62, 74.79, 65.82, 31.59, 31.45, 31.09.

MS: 248(38), 230(16), 215(100), 200(28), 87(28), 170(50), exact mass calcd for $C_{14}H_{16}O_2S$ *m/z* 248.3392 obsd *m/z* 248.080

4.3 General Procedure For Thermal Cyclizations

The enediyne (0.20 mmol) was dissolved in benzene (1.0 mmol) with Adogen phase transfer 464 catalyst (0.02 mL) and degassed with N_2 for 2 minutes in a vial. In a round bottomed flask, aqueous 10% NaOH (1.0 mL) with $NaBH_4$ (15 mg, 0.40 mmol) and hydrazine monohydrate (0.05 mL) were degassed with N_2 for 2 minutes. The benzene solution and the tellurium powder (28 mg, 0.22 mmol) were added to the aqueous solution and the mixture was clamped in a sonicating bath at 40^{0}C for 6 hours (with N_2

balloon). The mixture was rinsed into separatory funnel (methylene chloride) and the organic layer was washed with water (2 X 5 mL) and bleach (2 X 2 mL). The organic layer was dried over magnesium sulphate and rinsed through a thin pad of silica gel using methylene chloride.

4.4 General Procedure For Photochemical Cyclizations

A solution of enediyne (0.20 mmol) and 1,4-cyclohexadiene (160 mg, 0.19 mL, 2.0 mmol) was combined in quartz reaction vessel with methylene chloride (4.0 mL). The solution was degassed for 2 minutes with argon. The reaction mixture was irradiated for five hours using a mercury vapor arc lamp. Then the mixture was examined for products using GC-MS.

4.5 General Procedure For Competitive Rate Reactions

The intermolecular competition was carried out using 1 equivalent each of iodobenzene and the substituted iodobenzene in the presence of 0.05 equivalents of TMS-acetylene(0.07 mL), 2 mol % Pd (24.0 mg, 0.02 mmol) and 6 mol % CuI(24.0 mg, 0.06 mmol), THF (2.50 mL). After a standard reaction time of 5 hours, a GC of the mixture was run (internal standard biphenyl) and the relative rates of reactivity were calculated.

4.6 Spectroscopic Characterization For Competitive Rate Reactions

1-Phenyl-2-trimethylsilylethyne:

^{1}HNMR($CDCl_3$): δ 7.62-7.4 (m, 5H, Ph), 0.20-0.04 (m, 9H, CH_3).

^{13}CNMR: δ 133.67, 132.58, 129.11, 129.05, 89.63, 84.07, 2.49.

IR(neat): 2200, 2100, 1790, 1650, 1510, 1290, 1200, 1100, 870, 710.

MS: 174(65), 160(55), 159(100), 129(45), 105(48) exact mass calcd for $C_{11}H_{14}Si$ *m/z* 174.07 obsd *m/z* 174.

***m*-(2-trimethylsilylethynyl)Phenol (97):**

^{1}HNMR ($CDCl_3$): δ 7.07 (s, 1H), 6.96 (d, J= 7.0 Hz, 1H), 6.90 (t, J= 7.5 Hz, 1H), 6.84 (d, J= 8.0 Hz, 1H), 4.89 (br. s., 1H), 0.13 (s, 9H).

^{13}CNMR ($CdCl_3$): δ 155.2, 129.5, 124.3, 118.7, 116.2, 104.9, 94.5, 89.78, 0.0.

IR (neat): 3400, 2860, 2060, 1545, 1535, 1200, 1005, 800.

MS: 190 (19.5), 175 (100), 145 (4.6), 88 (3.6).

***p*-(2-trimethylsilylethynyl)Phenol (98):**

^{1}HNMR ($CDCl_3$): δ 7.70-7.29 (m, 4H), 0.219-0.189(s, 9H, $Si(CH_3)_3$).

^{13}CNMR($CDCl_3$): δ 155.8, 141.7, 133.6, 115.3, 105.0, 92.3, 0.0.

IR(neat): 2890, 2178, 2067, 1790, 1650, 1482, 1320, 1178, 1100, 833.

MS: 190.04(45), 175(100), 144(10), 115(9), 87(13), exact mass calcd for $C_{11}H_{14}OSi$ *m/z* 190.08 obsd *m/z* 190.04.

_m_-(2-trimethylsilylethynyl)toluene (99):

^{1}HNMR ($CDCl_3$): δ 7.36 (s, 1H), 7.40 (t, J= 7.3 Hz, 1H), 7.18 (d, J= 7.2 Hz, 1H), 2.32 (s, 3H), 0.26 (s, 9H).

^{13}CNMR ($CDCl_3$): δ 138.0, 132.4, 129.3, 129.0, 128.2, 128.0, 115.4, 93.8, 34.9, and 0.0.

IR (neat): 3030, 2970, 2845, 2145, 1595, 1483, 1248.

MS: 188 (17.8), 173 (100), 143 (5.4).

_p_-(2-trimethylsilylethynyl)toluene (100):

^{1}HNMR ($CDCl_3$): δ 7.12- 6.84 (m, 4H), 2.21(s, CH_3), 0.002(s, 9H, $Si(CH_3)_3$).

^{13}CNMR ($CDCl_3$): δ 138.60, 131.83, 128.91, 119.98, 105.30, 93.20, 30.92, 0.07.

IR(neat): 3000, 2100, 1510, 1253, 1050, 873.

MS: 188.11(27), 173.08(100), 143(7), exact mass calcd for $C_{12}H_{16}Si$ *m/z* 188.10 obsd *m/z* 188.114.

_m_-(2-trimethylsilylethynyl)benzonitrile (101):

MS: Exact mass calcd for $C_{12}H_{13}SiN$ *m/z* 199.3274, obsd *m/z* 199.

Spectra were compared to the literature values[64].

_p_-(2-trimethylsilylethynyl)benzonitrile (102):

^{1}HNMR ($CDCl_3$): δ 7.49-7.31(m, 4H), 0.008-(-) 0.007 (m, 9H, $Si(CH_3)_3$).

^{13}CNMR ($CDCl_3$): 135.54, 131.87, 129.39, 118.28, 112.99, 102.49, 97.67, 0.021.

IR(neat): 2990, 2849, 2220, 2183, 1600, 1470, 1389, 1275, 900, 850.

MS: 199(95), 184(100), 154(90), 129(55), 103(70), 77(68), exact mass calcd for $C_{12}H_{13}SiN$ *m/z* 199.3274, obsd *m/z* 199.

_m_-nitro(2-trimethylsilylethynyl)benzene (103):

^{1}HNMR ($CDCl_3$): δ 8.18 (dt, J= 8.2, 1.2 Hz, 1H), 7.75 (dt, J= 8.0 Hz, 1H), 7.49 (t, J= 6.6 Hz, 1H), 7.22 (s, 1H), 0.26 (s, 9H).

^{13}CNMR ($CDCl_3$): δ 148.0, 137.6, 129.3, 126.9, 125.0, 122.9, 102.1, 97.8, 0.0.

IR (neat): 2900, 2840, 2155, 1455, 1245.

MS: 219 (7.0), 204 (100), 158 (22.0), 143 (13.0).

_p_-nitro(2-trimethylsilylethynyl)benzene (104):

^{1}HNMR ($CDCl_3$): δ 7.62-7.19(m, 4H), 0.126-0.002(s, 9H, $Si(CH_3)_3$).

^{13}CNMR ($CDCl_3$): δ 132.66, 132.57, 129.11, 129.02, 94.34, 81.29, 2.45.

IR(neat): 3000, 2161, 1600, 1508, 1430, 1120, 875.

MS: 219.033(23), 204(100), 158(30), 143(14), exact mass calcd for $C_{11}H_{13}SiNO_2$ *m/z* 219.072 obsd *m/z* 219.03.

_m_-α,α,α-trifluoro(2-trimethylsilylethynyl)toluene (105):

^{1}HNMR ($CDCl_3$): δ 7.76 (t, J= 5.0 Hz, 1H), 7.36 (d, J= 7.5 Hz, 1H), 7.32 (s, 1H), 7.27 (d, J= 7.0 Hz, 1H), 0.32 (s, 9H).

^{13}CNMR ($CDCl_3$): δ 132.7, 127.5, 123.0, 122.6, 121.5, 120.9, 103.9, 101.9, 100.7, 0.0.

IR (neat): 2960, 2160, 2060, 1489, 1430, 1330, 1330, 1250, 1135, 1070, 895.

MS: 242 (8.5), 227 (100), 197 (5.1).

p-α,α,α-trifluoro(2-trimethylsilylethynyl)toluene (106):

^{1}HNMR ($CDCl_3$): δ 7.41-6.99 (m, 4H), 0.175(s, 9H, $Si(CH_3)_3$).

^{13}CNMR for ($CDCl_3$): 132.7, 127.5, 123.0, 122.6, 103.9, 101.9, 100.7, 0.0.

IR(neat): 1710, 1600, 1500, 1393, 1242, 1200, 1000.

MS: 242.04(37), 227.01(100), 196.97(16), 164.08(9), 151(7), 88(8), exact mass calcd for $C_{12}H_{13}SiF_3$ *m/z* 242.3159 obsd *m/z* 242.04.

***m*- (2-trimethylsilylethynyl)anisole (107):**

^{1}HNMR ($CDCl_3$): δ 7.39 (dd, J= 9.0, 2.4 Hz, 1H), 7.26 (s, 1H), 7.13 (t, J= 9.0 Hz, 1H), 7.06 (dd, J = 8.5, 2.4 Hz, 1H), 3.36 (s, 3H), 0.37 (s, 9H).

^{13}CNMR ($CDCl_3$): δ 139.5, 134.3, 130.1, 122.4, 120.3, 110.09, 101.1, 98.2, 56.0, 0.0.

IR (neat): 2995, 2950, 2150, 1580, 1480, 1248, 1155.

MS: 204 (27), 189 (100), 146 (8.0).

***p*- (2-trimethylsilylethynyl)anisole (108):**

^{1}HNMR ($CDCl_3$): δ 7.22-7.07(m, 4H), 3.61(s, CH_3), 0.48(m, 9H, $Si(CH_3)_3$).

^{13}CNMR ($CDCl_3$): δ 159.7, 133.98, 114.29, 113.7, 105.68, 92.3, 55.78, 0.575.

IR(neat): 2997, 2850, 2200, 2089, 1600, 1510, 1250, 1180, 1075, 875.

MS: 204.04(62), 189.01(100), 173(18), 146(18), 94.5(10), exact mass calcd for $C_{12}H_{16}SiO$ *m/z* 204.097 obsd *m/z* 204.04.

p-(2-trimethylsilylethynyl)ethylbenzene (110):

^{1}HNMR($CDCl_3$): δ 7.30-7.04(dd, 4H), 2.55(q, CH_2), 1.30(t, CH_3), 0.16(s, $Si(CH_3)_3$).

^{13}CNMR($CDCl_3$): δ 144.87, 131.90, 127.71, 120.23, 105.34, 93.16, 30.88, 15.30, 0.55.

IR(neat): 2910, 2143, 1393, 1391, 1383, 1387, 1283, 1200, 1069.

MS: 202(30), 187(100), 153(10), 125(10), 103(20), 77(14), exact mass calcd for $C_{13}H_{18}Si$ *m/z* 202.34 obsd m/z 202.

m-(2-trimethylsilylethynyl)aniline (111):

^{1}HNMR ($CDCl_3$): δ 7.65 (t, J= 8 Hz, 1H), 6.86 (dm, J= 8 Hz, 1H), 6.78 9 (s, 1H), 6.63 (dm, J= 8.0 Hz, 1H), 3.52 (s broad, 2H, NH_2), 0.22 (s, 9H, CH_3).

^{13}CNMR ($CDCl_3$): δ 146.14, 129.91, 122.47, 118.24, 115.63, 123.78, 105.38, 93.47, 0.04.

IR (neat): 3465, 3374, 2156.

p-(2-trimethylsilylethynyl)aniline (112):

^{1}HNMR ($CDCl_3$): δ 7.75-6.61(m, 4H), 5.23(s, NH_2), 0.20-0.09 (m, 9H, $Si(CH_3)_3$).

^{13}CNMR ($CDCl_3$): δ 133.45, 130.90, 125.85, 124.79, 118.15, 114.69, 1.47.

IR(neat): 3400, 2897, 2100, 1625, 1575, 1275, 1250, 1100, 800.

MS: 189.089(40), 174.06(100), 144.07(8), 130(6), 87(7), 75(6), exact mass calcd for $C_{11}H_{15}NSi$ *m/z* 189.09 obsd *m/z* 189.08.

APPENDIX

GC DATA

Table 5 – Competitive Rate Experiment Data For Iodotoluene Versus Iodobenzene

TMS-acetylene Used	Peak Area		Peak area	
	meta-	H-	*para-*	H-
	11.67(RT)	9.34(RT)	11.87(RT)	9.33(RT)
0.05 Equivalent	4818	5102	2843	7975
Biphenyl	Amount	Peak Area	Amount	Peak Area
	0.0004 gm	268480	0.0003 gm	711600

Table 6 – Competitive Rate Experiment Data For Iodoanisoles Versus Iodobenzene

TMS-acetylene Used	Peak Area		Peak Area	
	meta-	H-	*para-*	H
	14.43(RT)	9.32(RT)	14.90(RT)	9.34(RT)
0.05 Equivalent	13873	19358	3829	14932
Biphenyl	Amount	Peak Area	Amount	Peak Area
	0.0006 gm	244440	0.0005 gm	141080

Table 7 – Competitive Rate Experiment Data for Iodoanilines versus Iodobenzene

TMS-acetylene Used	Peak Area		Peak Area	
	meta-	H-	*para-*	H
	16.19(RT)	9.32(RT)	16.74(RT)	9.32(RT)
0.05 Equivalent	5708	30998	3744	46172
Biphenyl	Amount	Peak Area	Amount	Peak Area
	0.0004 gm	216940	0.0004 gm	196400

Table 8 – Competitive Rate Experiment Data for Iodophenol versus Iodobenzene

TMS-acetylene Used	Peak Area		Peak Area	
	meta-	H-	*para-*	H
	16.42(RT)	10.28(RT)	16.20(RT)	9.34(RT)
0.05 Equivalent	4091	50573	3319	11905
Biphenyl	Amount	Peak Area	Amount	Peak Area
	0.0004 gm	299970	0.0005 gm	134430

Table 9 – Competitive Rate Experiment Data for Iodobenzotrifluorides versus Iodobenzene

TMS-acetylene Used	Peak Area		Peak Area	
	meta-	H-	*para-*	H
	9.02(RT)	9.35(RT)	9.16(RT)	9.31(RT)
0.05 Equivalent	59766	9894	28939	3348
Biphenyl	Amount	Peak Area	Amount	Peak Area
	0.0004 gm	236120	0.0002 gm	105070

Table 10 – Competitive Rate Experiment Data for Iodonitrobenzenes versus Iodobenzene

TMS-acetylene Used	Peak Area		Peak Area	
	meta-	H-	*para-*	H
	16.97(RT)	9.36(RT)	17.21(RT)	9.39(RT)
0.05 Equivalent	45922	21834	71286	2083
Biphenyl	Amount	Peak Area	Amount	Peak Area
	0.0005 gm	149510	0.0007 gm	532970

Table 11 – Competitive Rate Experiment Data For Iodoanilines versus Iodobenzene

TMS-acetylene Used	Peak Area		Peak Area	
	meta-	H-	*para-*	H
	15.76(RT)	10.26(RT)	15.74(RT)	10.09(RT)
0.05 Equivalent	47118	13733	57319	10174
Biphenyl	Amount	Peak Area	Amount	Peak Area
	0.0003 gm	450330	0.0003 gm	370670

Calculations and Kinetic Treatment for Competitive Rate Reactions:

The relative rates were calculated by allowing a mixture of the iodides (substituted [S] and unsubstituted [US]) to react with a small amount of the alkyne [A].

$$S + A \rightarrow SA$$

$$US + A \rightarrow USA$$

The competing reactions are assumed to have the same rate law:

$$-d[S]/dt = d[SA]/dt = k_S[S]^s[A]^n$$

$$-d[US]/dt = d[USA]/dt = k_{US}[US]^s[A]^n$$

Dividing one equation by the other we obtain:

$$d[SA]/d[USA] = k_S/k_{US}\,([S]/[US])^s \text{ ---------- [1]}$$

In this experiment, S and US are the two iodides competing for a small amount of alkyne. The reaction can be treated as pseudo-first order so:

$$d[SA]/d[USA] = k_S/k_{US}\,[S]/[US] \text{ ---------- [2]}$$

Assuming the ratio [S]/[US] is approximately constant, and equal to the ratio $[S]_0/[US]_0$, equation [2], after integration, becomes:

$$[SA]_t/\,[USA]_t = k_S/k_{US}[S]_0/[US]_0$$

or

$$(nSA/nUSA)t = k_S/k_{US}\,(nS0/nUS0) \text{ ---------- [3]}$$

With $k_S/k_{US} = k_{relative}$

Thus, the relative rate constants could be calculated from equation [3] from GC results. The relative constant are then fit to Hammett equation [with σ_p], **Graph 7**.

$$\log k_{relative} = \log\,[k_S/k_{US}] \text{ ----------[4]}$$

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