

The S_{RN}1 Reactivity of Selected
Aromatic Diazines

by

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I. Introduction

Formation of carbon-carbon bonds is the mainstay of the synthetic organic chemist. Unfortunately, there is no general method for making all types of carbon-carbon bonds, and for that reason the methodology for making these bonds is wide and varied.

One particularly fascinating problem in organic synthesis involves the utilization of nucleophilic aromatic substitution for C-C bond formation. Historically nucleophilic substitutions at carbon sites bearing "leaving groups" or nucleofuges* has been very useful for making bonds of this type. However, very early in the course of investigations of nucleophilic substitutions it was found that substitutions by nucleophiles at aromatic and other sp^2 hybridized carbons are relatively difficult and are "unreactive" under conditions that allow facile substitutions on their aliphatic sp^3 counterparts.²

Explanations for this lack of reactivity center around the arguments:

1) the overlap of the electron lone pairs on the nucleofuge with the p orbitals of vinylic systems accounts for a greater stabilization of the ground state molecule than the transition state for nucleophilic displacement.

*Nucleofuge is a term introduced by Mathieu and is widely used instead of "leaving group" or

2) the fact that in the transition state the energy required to change the hybridization of the sp^2 carbon to sp^3 is large. These ideas are supported by the fact that aromatic carbon-halogen bonds are unusually short (and all other things equal, stronger than sp^3 carbon-halogen bonds), and the dipole moments of aryl halides are small. Therefore, aromatic compounds should show thermodynamic and kinetic stability under "normal" reaction conditions. "Normal" conditions being defined as those that allow S_N1 and S_N2 type mechanisms to operate in aliphatic systems.

For many years, nucleophilic aromatic substitution was viewed as being a synthetic route to be avoided, if possible. The requirement for strong nucleophiles, high temperatures, or activated substrates promoted the development of electrophilic aromatic substitution in the early days of synthetic organic chemistry. Investigations into aromatic electrophilic substitutions reactions were confined primarily to benzoaromatics during the early part of the century. This was probably due to the ready availability of these simple aromatics and the resistance of most nitrogen aromatics towards clean reactions with electrophiles. After the introduction of nonaqueous solvents and strongly basic media; nucleophilic aromatic substitution became a subject of intense research, and several new, unpredicted mechanisms emerged. These mechanisms are detailed in the following sections.

II. Mechanisms of Nucleophilic Substitution With Various Types of Aromatic Substrates

As previously mentioned aromatic systems are resistant to nucleophilic substitution. However, when treated with enough vigor the system can be forced to undergo substitution. The more "activated" the aromatic ring the less forcing these conditions must be.

In the following sections the various types of mechanisms that appear to be operative in aromatic nucleophilic substitutions will be discussed. The mechanism of substitution for a particular reaction depends primarily upon the structure of the aromatic substrate and the nucleophile. To a lesser extent the mechanism is affected by the reaction conditions (solvent, temperature, etc.). A convenient categorization of these mechanisms is by aromatic substrate.

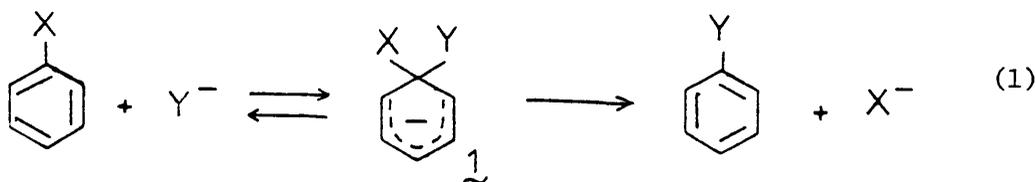
Systems that are included cover benzoaromatics, pyridine, pyrimidine, pyridazine, pyrazine, quinoline, isoquinoline, quinoxaline, quinazolines, cinnoline, and phthalazine. Also the relative reactivities of these systems towards nucleophilic substitutions will be discussed based on available data from the chemical literature.

A. Benzoaromatic Substitutions

By analogy to the aliphatic halides, early studies aimed logically at forcing nucleophilic substitutions of haloaromatics into reaction mechanism categories and their implied conditions that we now know as S_N2 and S_N1 . Recently, different reaction pathways that do not fit S_N1 and S_N2 mechanisms have emerged and been partially explored. First we will mention the aromatic, or more appropriately, the S_NAR2 mechanism.

1. Bimolecular Nucleophilic Substitution at Aromatic Carbon(S_NAR2, AE_N)

Concerted nucleophilic displacements at aromatic carbon in the manner of S_N2 substitution at aliphatic carbon does not appear to occur. Instead, a two-step mechanism often takes place. The rate determining step is addition of the nucleophile to form a "new" bond before the "old" bond is broken as depicted below in eq. 1.

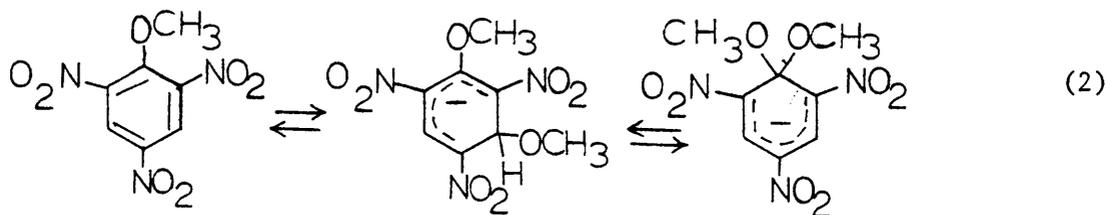


This bimolecular step involving both the nucleophile and the aromatic ring gives the mechanism its name, S_NAR2 (substitution, nucleophilic, aromatic, bimolecular). This mechanism is an addition of the nucleophile followed by elimination of the nucleofuge, and is also called, S_N(AE_N) (Substitution, Nucleophilic, Addition, Elimination normal). Abbreviated forms of these acronyms include S_NAR, S_N(AE), AE_N, etc.

Formation of intermediates such as 1 appear to have existence in even the most rapid of displacements. In fact, as Meisenheimer showed, they can even be isolated in certain cases.³ This type of σ-complex (addition compound) is thus termed a Meisenheimer complex, or by some, a Jackson-Meisenheimer complex.⁴ Reviews dealing with σ-complexes have been published,^{5,6} as well as their mention in reviews of nucleophilic aromatic substitution.^{7,8,9}

Two σ-complexes may be formed in equilibrium during a substitution reaction by attack of the nucleophile at two different activated sites.

An example of this type of behaviour is given in eq. 2.^{5,6} However, if attack at one of the sites is reversible, then formation of this σ -complex does not affect the overall substitution process except by decreasing the effective concentrations of nucleophile and substrate.

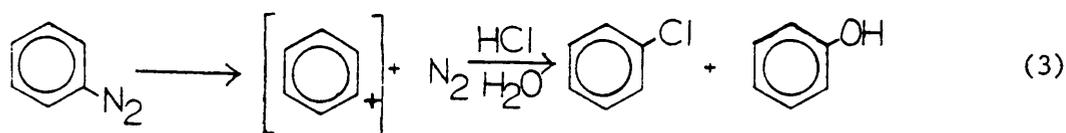


The S_NAR mechanism is seldom encountered in unactivated aryl halides; although in highly polar aprotic solvents with good nucleophiles it has been reported to occur with certain unactivated benzoaromatics.¹¹ Activating groups include functionalities that will stabilize the developing negative charge on intermediate 1 by inductive or resonance effects. Typical activating groups include nitro, keto, or diazonio functions in ortho or para positions. In passing let us note that the rate of reaction in a given series parallels the increasing electronegativity of nucleofuge.^{7,8}

2. Unimolecular Aromatic Nucleophilic Substitution (S_N1)

Tertiary aliphatic halides undergo first-order nucleophilic substitution reactions designated as S_N1 . This process yields a carbonium ion in the rate-determining unimolecular decomposition step (S_N1). Although halobenzenes do not react in this manner, even under the most forcing conditions, they can be considered to be structurally similar to tertiary halides. The strong carbon-halogen

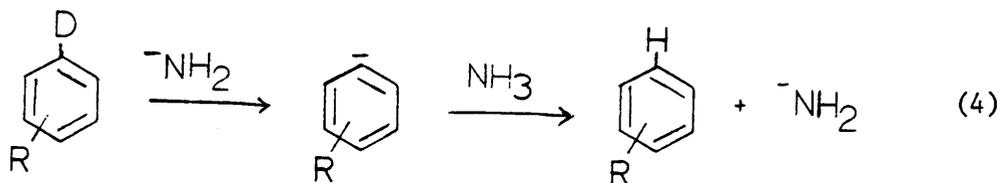
bond and the apparent instability of the resulting phenyl cation make this mechanism difficult to be established. The only practical method of generating the phenyl cation is through the thermal decomposition of the aryldiazonium ion. However, nucleophilic displacements of the diazonio function (eq. 3) do not appear to proceed exclusively through an aryl cation.¹²



For example, evidence has been put forward by Bunnett for competing ionic and radical mechanisms.¹² Other evidence in support of the phenyl cation has been published recently.¹³

3. Nucleophilic Attack on Hydrogen

Strong bases may attack hydrogen according to eq. 4 given below.²

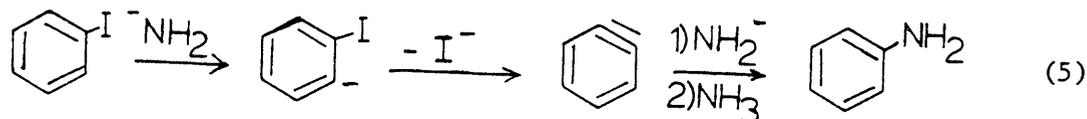


This may be encountered when the anion formed is stabilized by two or more halogens and alternate reaction pathways are suppressed.

4. The Benzyne Mechanism (EA)

Reviews on this subject have been published,^{14,15} and the topic is much too broad to discuss in detail here. Briefly, as in the

above mechanism (Sect. 3), if the nucleophile attacks a hydrogen on the ring adjacent to a potential leaving group, to form a *o*-halophenyl anion, elimination of the nucleofuge can occur to form an aryne or as sometimes called, didehydrobenzene. (Eq. 5).



This benzyne intermediate can then add a nucleophile to form an aryl anion, with subsequent protonation resulting in overall substitution of the nucleofuge. Since this process involves elimination of the nucleofuge followed by addition of the nucleophile, it is sometimes termed the elimination - addition (EA) mechanism.

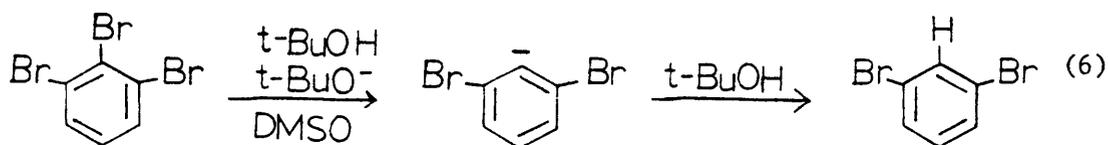
It is interesting to note that in the EA mechanism the "molecular memory" of the position of the halogen is lost. In the absence of directive effects of additional substituents on the ring, addition can take place at either terminus of what is apparently a triple bond within the aromatic nucleus. This can lead to products where the nucleophile enters a position adjacent to the position originally occupied by the nucleofuge. Formation of this isomeric product is classified as *cine* substitution. This is one of the most characteristic features of the benzyne mechanism.

The ease of halide expulsion is $\text{I} > \text{Br} > \text{Cl} > \text{F}$. Solvents that are poor proton donors serve as the best reaction media for obvious reasons.

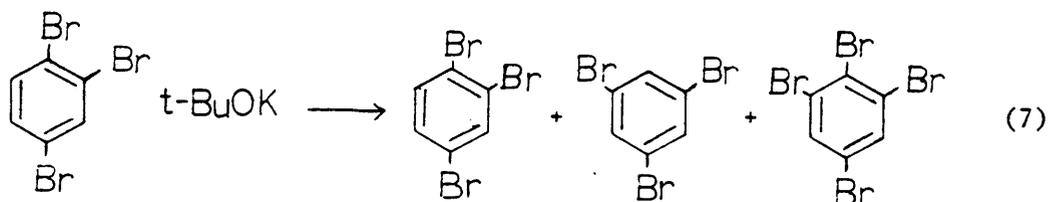
However, they must be capable of solvating the halide anion reasonably well; otherwise, the expulsion of the halide is slow. Solvents such as ammonia work very well in these respects.

5. Nucleophilic Attack on Halogen (Metal-Halogen Exchange)

Nucleophiles may attack the leaving group (nucleofuge) to produce the halogenated nucleophile and the aromatic anion (eq. 6).¹⁶

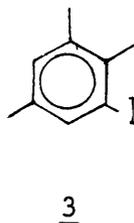
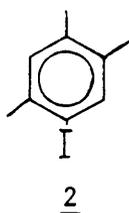


Typically attacks of this kind are classified as metal-halogen exchanges, and occur most often when very strong bases such as n-butyllithium are used. In other cases weaker bases can be used to cause sequences such as the "base-catalyzed halogen dance" shown in eq. 7.²



6. Electron Transfer Reactions (S_{RN}1)

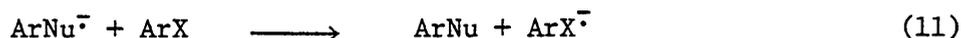
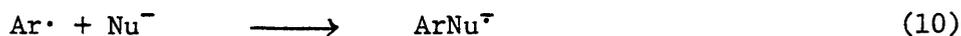
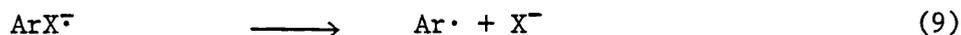
In the course of an investigation to probe the benzyne mechanism in the dehydrohalogenation of 5- and 6-iodopseudocumenes (2 and 3) with KNH₂ in liquid ammonia, Bunnett and co-workers noted that more



of the direct substitution products were obtained than could be accounted assuming a common aryne intermediate.¹⁷ Further investigation into this nonrearranging reaction revealed that it was occurring via a radical chain mechanism. Addition of tetraphenylhydrazine (a radical scavenger) mostly suppressed the chain reaction, and addition of potassium metal served to steer the reaction entirely to unrearranged products (ipso substitution). By analogy to a radical chain mechanism proposed earlier by Kornblum and Russell for substitution at aliphatic sites,¹⁸ Bunnett proposed basically the same mechanism for this mode of aromatic substitution and termed it $S_{RN}1$, Substitution, Radical Nucleophilic Unimolecular.

Evidence rapidly accumulated to lend substance to this hypothesis and soon the high synthetic potential of the process became evident to workers in the field. Reviews of the mechanistic features and synthetic applications have recently been published.^{19,20}

Briefly, the overall reaction sequence may be written as follows:

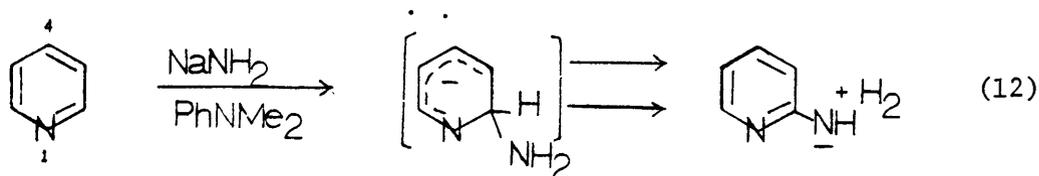


The chain initiation step as shown in eq. (8) reduces the aromatic substrate to the radical anion. Decomposition of the radical anion into an aromatic radical and halide anion occurs (eq. 9). This step is analogous to the well known S_N1 reaction of a tertiary aliphatic halide. The aromatic radical generated combines with the nucleophile

to form the radical anion of the substitution product (eq. 10). In the last of the propagating steps, the radical anion of the substitution product transfers an electron back to the aromatic substrate (eq. 11). The resulting radical anion can reenter the chain as in eq. (8). Further discussion of the implications of this sequence will be discussed in Section IV.

B. Pyridine Substitutions

Substitutions involving π -deficient nitrogen heterocycles such as pyridine are relatively easy compared to benzoaromatic analogs.²¹ As an example the Chichibabin reaction, which involves the interaction of NaNH_2 with pyridine to form 2-aminopyridine (eq. 12), points to a fundamentally different reactivity of nitrogen heterocycles.²¹

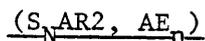


In this example overall substitution of hydride can be performed on pyridine; a feat that is very rare in benzoaromatic chemistry.²²

The Chichibabin reaction also illustrates another basic difference between the azaaromatics and benzoaromatics. Addition to the heterocycle is much more facile than in comparable benzoaromatics. The reactions of pyridine have been likened more to the chemical reactions of nitrobenzene than to benzene itself. In fact, in the case of increased ring aza substitution, the effects of additional nitrogen substitution seem to be roughly additive. Two aza substituents seem to activate the ring twice

as much as one aza substituent. This will become more obvious in the following sections.

1. Bimolecular Nucleophilic Substitution at Aromatic Carbon



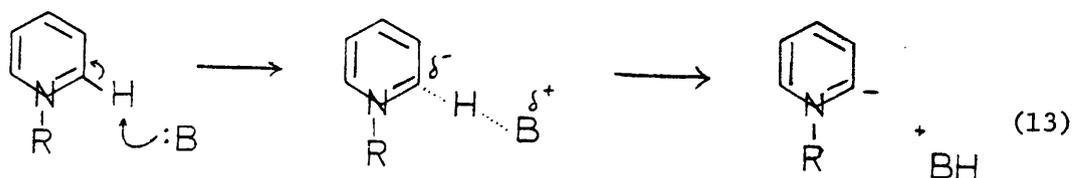
Mechanisms similar to the $\text{S}_{\text{N}}\text{AR}_2$ are often observed with substituted pyridines. Halogens and nitrogen substituents at the 2, 4, or 6 positions of pyridine are readily displaced. Halogens at the 3 or 5-position of pyridine resemble halobenzenes in their properties. Substituents at the 4-position of pyridine seem to be the most reactive in many nucleophilic substitutions. Presumably this is due to the decreased repulsion of the entering nucleophile and the nitrogen lone pair on the ring.

2. Unimolecular Aromatic Nucleophilic Substitution ($\text{S}_{\text{N}}1$)

The $\text{S}_{\text{N}}1$ mechanism has not been observed in the pyridine series, although calculations indicate that the pyridyl cation should be more stable than the phenyl cation.²³

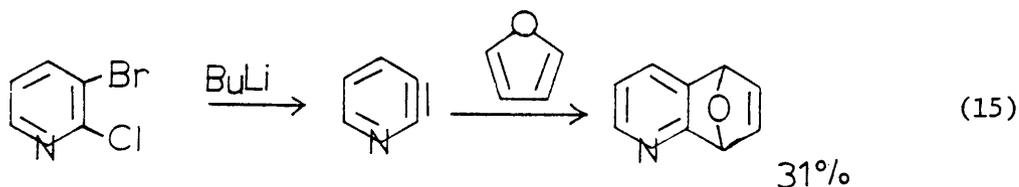
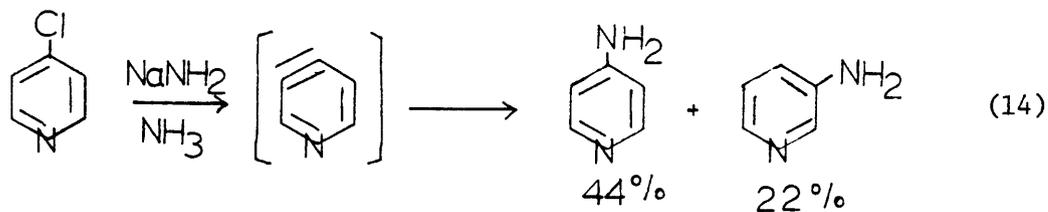
3. Nucleophilic Attack on Hydrogen

Hydrogen-deuterium exchange in pyridine derivatives was once assumed to involve intermediates such as σ -complexes, but now the accepted explanation is the mechanism diagrammed below (eq.13) to a pyridyl carbanion.^{24,25,26}



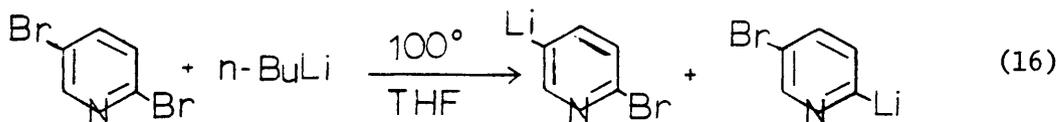
4. The Pyridyne Mechanism (EA)

With strongly basic nucleophilic reagents the 3,4-pyridyne (hetaryne or EA) mechanism can be obtained with either 3- or 4-halopyridines. The transient 3,4-pyridyne can react to form products substituted at either the 3- or 4-position (eq. 14). In cases where both 2,3-pyridyne and 3,4-pyridyne can be formed, evidence indicates that the 3,4-pyridyne is produced.²⁷ In the case of 3-bromo-2-chloropyridine, treatment with n-butyllithium gives a product of apparently 2,3-pyridyne (eq. 15).²⁸



5. Nucleophilic Attack on Halogen (Metal-Halogen Exchange)

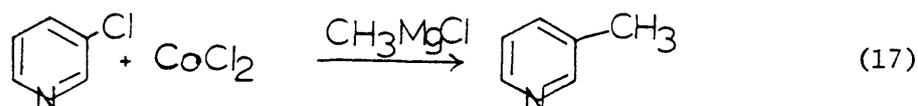
Nucleophilic attack on halogen can take place to form aryl lithiums. This is generally in competition with addition as illustrated below (eq. 16).²⁹



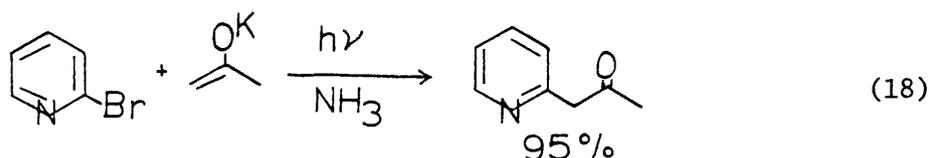
Such metal halogen exchanges have largely replaced pyridyl Grignard reagents as synthetic anions of pyridine.

6. Electron Transfer Reactions ($S_{RN}1$)

Electron transfer to coordinated pyridyl halides have been implicated in the following reaction (eq. 17).³⁰



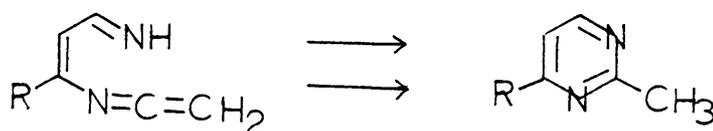
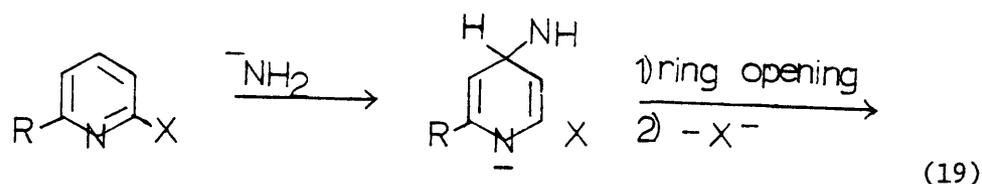
The $S_{RN}1$ mechanism has been investigated in the pyridine case.³¹ Substitutions of halogens on pyridine by ketone enolates, as well as other nucleophiles, take place under photostimulation in a manner more facile than that of benzoaromatics (eq. 18). Also of interest, is the lack of reduction products in reactions involving enolates possessing β -hydrogens. This reduction process is a significant drawback in analogous reactions with benzoaromatics.



7. Ring Transformations, S_{ANRORC}

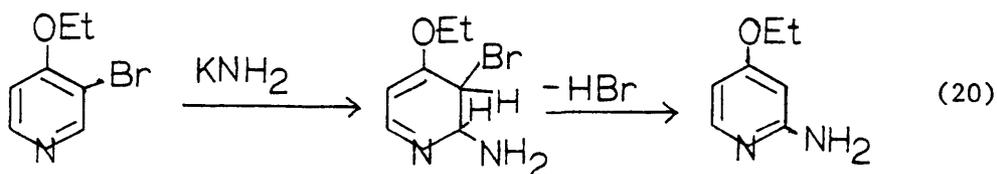
Although in many cases the results of this type of mechanism does not result in straight ipso substitution (or cine substitution), the mechanism is included. In some cases the attack of a nucleophile on a pyridine ring is followed by ring opening, which leads to an overall

ring transformation, as in the example show below (eq. 19).³² Mechanisms of this type are classified as S_N ANRORC (Substitution Nucleophilic Addition of the Nucleophile Ring Opening and Ring Closure).



8. Addition-Elimination Abnormal (AEa)

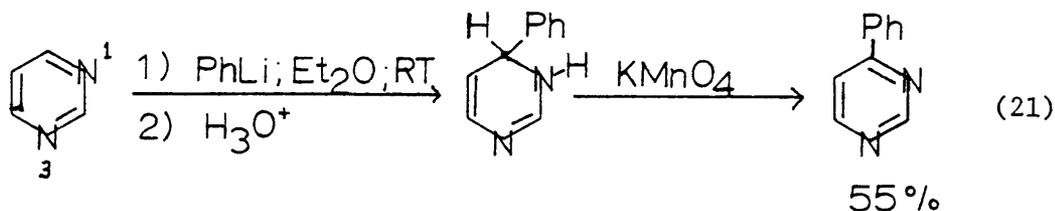
This mechanism is similar the AE_n mechanism described in Section II.A.1., but as previously mentioned the σ -complex formed by addition of the nucleophile to the aromatic molecule does not have to necessarily be at the carbon containing the nucleofuge. Attack at another position, then consumption of this intermediate could give the observed products (usually cine substitution). An example of a believed "abnormal" addition-elimination (AEa) reaction is given below (eq. 20).^{33,34}



C. Pyrimidine Substitutions

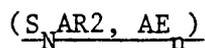
Pyrimidines are unique among the monocyclic diazines in that the 5 position of the ring is not α or γ to any ring nitrogen. Therefore, the activating influence of these heteroatoms is purely inductive, and by analogy to the β -position of pyridine, it is relatively unreactive. This is shown by the ability of pyrimidine to be electrophilically brominated at that position under comparatively mild conditions.³⁵

As with pyridine, the pyrimidine ring readily adds nucleophiles to the 4 position. With nucleophiles such as Grignard reagents, alkyllithium and aryllithium compounds, addition produces the dihydro-derivatives upon acid quench.³⁶ These addition compounds may then be oxidized to the aromatic system by a variety of oxidants. The dihydro-pyrimidine frequently requires more vigorous oxidizing conditions to achieve aromatization than dihydropyridines (eq. 21). This very



likely reflects the aromatic stabilization of pyrimidine versus that of pyridine.³⁶

1. Bimolecular Nucleophilic Substitution at Aromatic Carbon

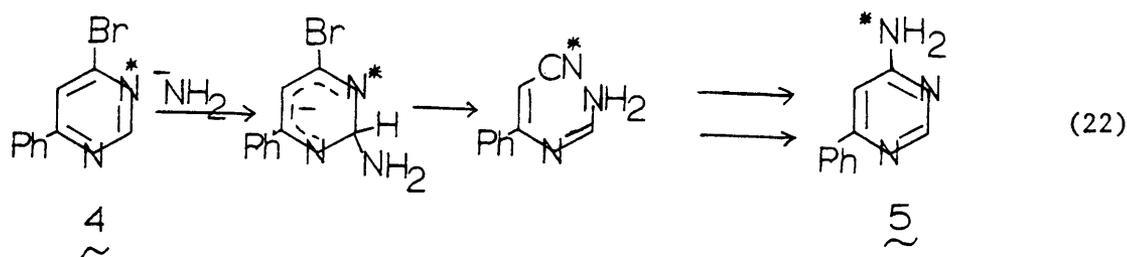


Because of the increased electron withdrawal of the additional aza-substitution in pyrimidine over that of pyridine, substitutions

by nucleophiles are much more facile in pyrimidine than in pyridine derivatives. With most nucleophiles the mechanism the literature data supports is a S_NAR reaction. This support is well founded in most cases, but new mechanisms for seemingly straightforward substitutions have been published. These mechanisms will be discussed in the following sections with reference to the more common S_NAR mechanism as needed.

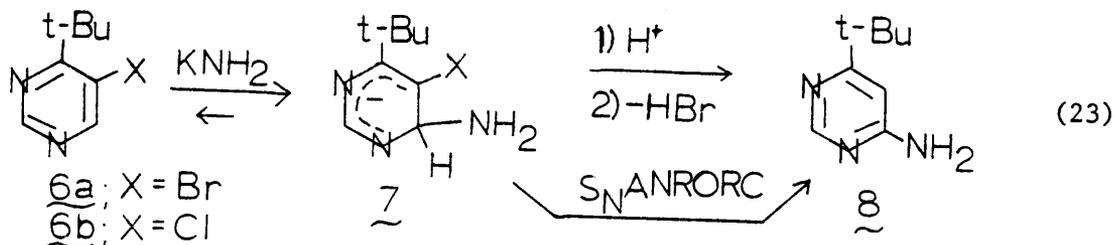
2. Ring Transformations ($S_NANRORC$)

The $S_NANRORC$ mechanism in pyrimidines has recently been reviewed by van der Plas.³⁷ Noteworthy is the fact that many of the ring-opening ring-closing reactions of pyrimidine are degenerate (or ipso) ring transformations. In other words, a pyrimidine ring undergoes the ring-opening, and the ring opened compound closes to a pyrimidine ring. An example of this type of reaction is that of 6-bromo-4-phenyl-1(3)-¹⁵N pyrimidine, 4, reacting with KNH_2 in ammonia (eq. 22).³⁷



By use of the labeled nitrogen, it was shown that the nitrogen that was in the ring was located outside the ring in the final substituted product (5).

It was proved by means of ^{15}N labeling experiments that two mechanisms are operative in the reaction of 6 with potassium amide in ammonia (eq. 23).³⁸ Thus, 49% of σ -adduct 7 reacts via an $\text{S}_{\text{N}}(\text{ANRORC})$ mechanism into the substituted product, 8. The remainder of adduct 7



undergoes protonation followed by loss of hydrogen bromide to yield 8 by what is an $\text{A}\text{E}_{\text{a}}$ mechanism. In the case of chloro derivatives, 6b, no $\text{S}_{\text{N}}(\text{ANRORC})$ mechanism was found to be operational. The alternative mechanism is the $\text{A}\text{E}_{\text{a}}$ or a Chichibabin type amination by loss of a hydride from the σ -adduct, 7. The possibility of a pyrimidyne intermediate has fallen into disfavor.³⁸

Another point on these mechanisms and their supporting evidence needs to be made. In the first example of $\text{S}_{\text{N}}(\text{ANRORC})$ with the 4-halopyrimidine (eq. 22) although the mechanism formulated shows the initial attack of the nucleophile to be at the 2-position of the pyrimidine, the ^1H NMR spectrum of the reaction mixture indicated a high yield of attack at the 6-position of the pyrimidine. This position of pyrimidine is the most reactive site toward nucleophilic attack, and thus lends support to σ -adducts at that position.

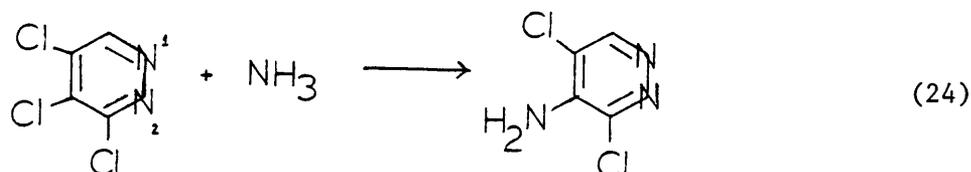
D. Pyridazine Substitutions

Pyridazines were obtained as early as 1886 by Fischer, but have not been investigated as thoroughly as other members of the diazine

family since they do not occur as natural products. In fact very few natural products are known in which two nitrogen atoms are adjacent to each other. Reviews and monographs that cover much of the chemistry of the pyridazine ring system are available.³⁹

Substitutions by nucleophiles occurs readily on pyridazine derivatives due to the two nitrogen atoms that greatly increase the Π -deficiency on the carbon atoms. For the same reason the molecule is resistant to attack by electrophilic reagents.

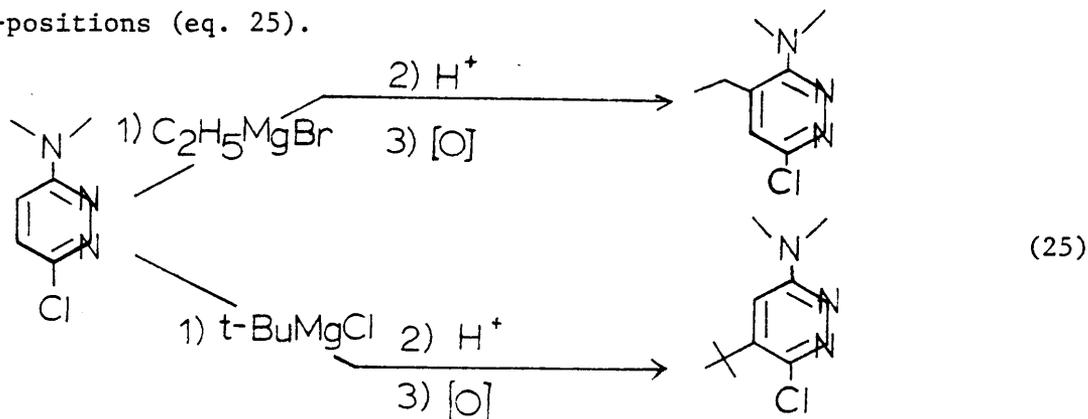
Nucleophilic substitution on halogenated pyridazines occurs without many problems. Because of decidedly different reactivity of the various chlorine atoms in a pyridazine containing two or more chlorine atoms, selected reaction at a particular site can be accomplished. For example, 3,4,5-trichloropyridazine undergoes selective replacement of the 4-halogen (eq. 24).⁴⁰



However, the reactivity of 3-chloropyridazine and 4-chloropyridazine appear to be approximately the same toward p-nitrophenoxide ion in methanol.⁴¹

Direct introduction of alkyl or aryl groups by organometallic reagents such as alkyl lithiums suffer from poor yields. Crossland⁴²

showed that in the case of 3-chloro-6-(dimethylamino)pyridazines reaction of Grignard reagents provided substitution at the 4- and 5-positions (eq. 25).



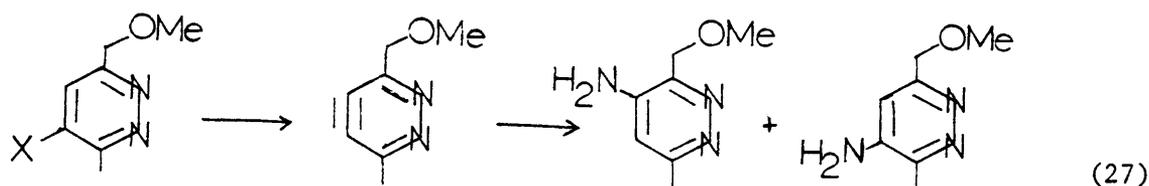
These reactions indicate that in the 3-chloropyridazines, at least, the 4-position is very prone to addition. In reaction with weaker nucleophiles, substitution at the carbon bearing the nucleofuge can be performed.⁴³

Substitution at the nucleofugic carbon can be accomplished in the presence of a catalytic amount of dichloro- 1,2-bis(diphenylphosphine) propane nickel, Ni(dppp)Cl_2 (eq. 26).⁴⁴ The role of the transition



metal complex in this case was not defined or mentioned.

A didehydropyridazine was implicated in the aminolysis of a substituted 4-halopyridazine (eq. 27).⁴⁵ The ratios of 4-substitution to 5-substitution did not change upon variation of the halogen; thus,

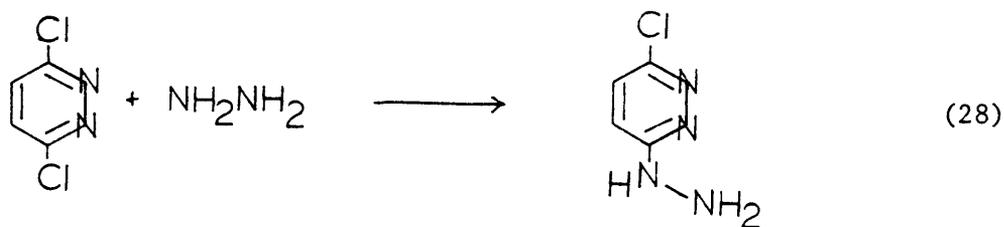


X = Cl, Br, or I

1 : 5

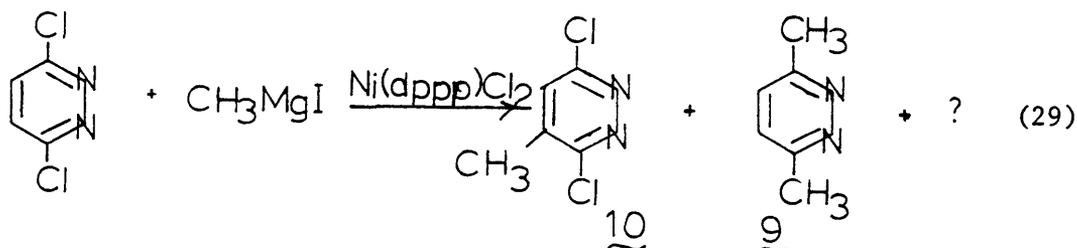
on this basis a AE type mechanism was eliminated from consideration.

Substitution on 3,6-dichloropyridazine can be carried out with weak nucleophiles with relative ease, as the following reaction illustrates (eq. 28).⁴⁶ However, with stronger nucleophiles the



attempted substitution of the nucleofuge is apt to present problems.^{44a}

Reaction of methylmagnesium iodide gave only 19% of the disubstitution (9) with no trace of the monosubstitution reaction product (eq. 29).

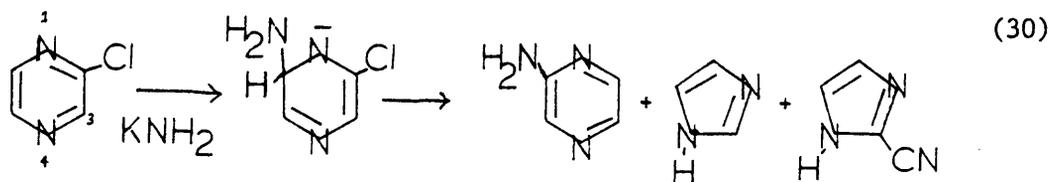


There was also isolated the 4-methyldichloropyridazine (10) and an unknown compound of m.p. 91.5-92.5. The unknown compound may be the hydrolyzed addition compound (see Sect. VI . G.4.).^{44a}

E. Pyrazine Substitutions

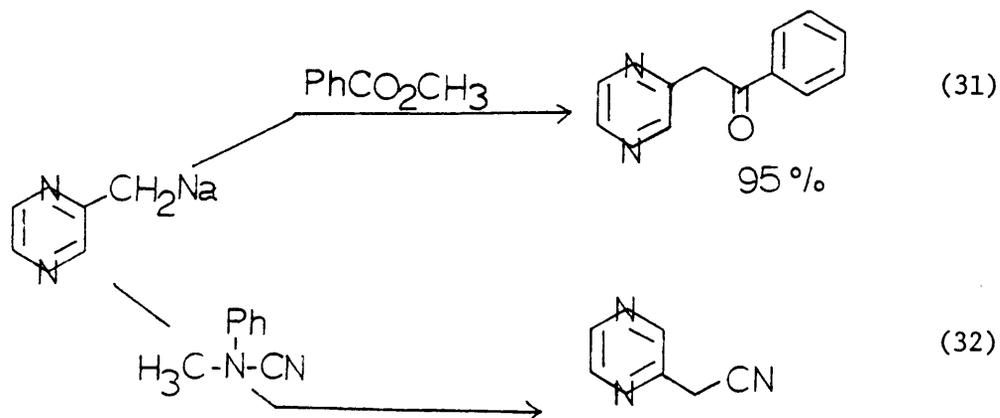
Pyrazines occur naturally, but not in great quantity. Many have been used by the drug industry and have a wide range of useful properties. Alkylpyrazines are important flavor constituents of roasted food products such as coffee, cocoa, and peanuts. They have also been detected in green bell peppers and green peas, and are assumed to be of major significance in the flavors of these vegetables.⁴⁷ Pyrazinyl ketones have also been found in roasted foods, and are also responsible for some of the odor and taste found in those cooked foods.⁴⁸

As with pyridazine and pyrimidine substitutions, nucleophilic displacements on pyrazine occur much more readily than on pyridine. The activating influence of the second aza substitution is very apparent in most substitution reactions. For example, the conversion of 2-chloro to 2-aminopyrazine by potassium amide does not proceed by an S_NAR mechanism (eq. 30).⁴⁹ Starting material labelled with nitrogen-15 gives substituted product with the label exocyclic to the ring. The $S_NANRORC$ mechanism is invoked to explain such results.

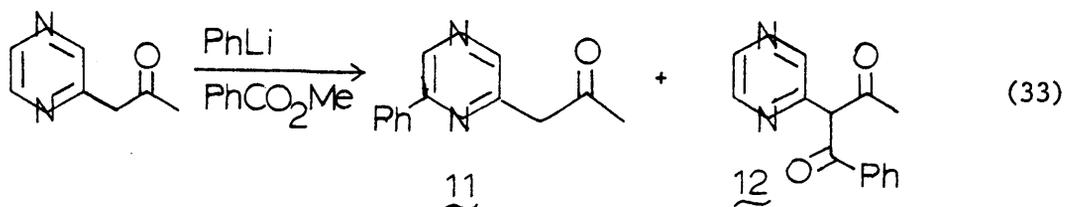


Organometallic reagents may give products of ring or side-chain substitution. The methyl group of a pyrazine is activated, and

it may upon treatment with a strong base afford a reactive carbanion. The pyrazylmethylsodium has been acylated with a wide range of esters (eq. 31).⁵⁰ Reaction of this anion with N-methyl-N-phenylcyanamide gives pyrazylacetonitrile (eq. 32).⁵¹

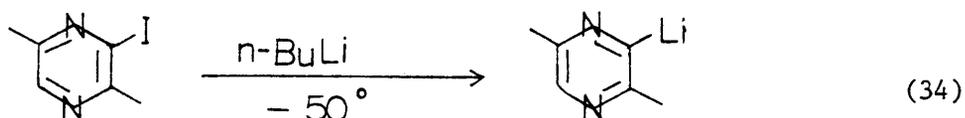


The reaction of acetonypyrazine with phenyllithium in the absence and presence of methyl benzoate has been studied. With phenyllithium alone, 11, the addition product was formed. In the presence of the ester a mixture of the two products, 11 and 12, were formed (eq. 33).⁵² Other reactions of methylpyrazines with strongly basic organometallic



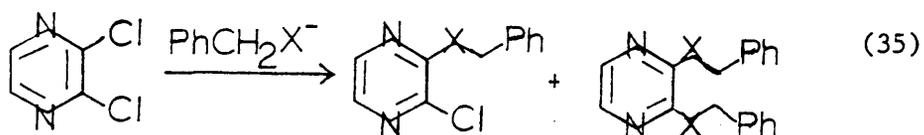
reagents have been discussed and reviewed.⁵³

Halogenated pyrazines show the expected reactivity and undergo transformations with nucleophiles under similar conditions to the halopyridines. Halogen-metal exchange is achieved by treatment with ethereal *n*-butyllithium (eq. 34).⁵⁴



Even the weak base, cyanide, can be induced to substitute for halogen in bromopyrazine.⁵⁵ Chloropyrazine undergoes the expected displacement reactions with ammonia, methylamine, dimethylamine, sodium methoxide, and sodium hydrogen sulfide to give the monosubstituted pyrazine.⁵⁶ Fluoropyrazine is significantly more reactive toward nucleophilic reagents than chloropyrazine, supporting an S_NAR mechanism for most reactions.

Mono- or disubstitution on 2,3-dichloropyrazine can be performed using an oxygen or sulfur nucleophile. The amount of substitution is dependent upon the amount of reagent used in the reaction (eq. 35).⁵⁷



The reaction of 2,6-dichloropyrazine with hydroxide and alkoxide ions has been investigated.⁵⁸

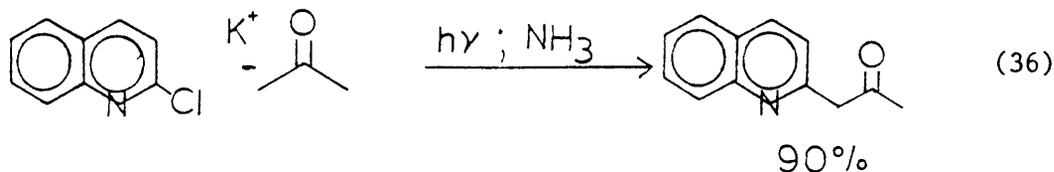
F. Quinoline and Isoquinoline Substitutions

Fusion of a benzene ring onto the pyridine nucleus yields quinoline or isoquinoline. This results in an increased reactivity toward



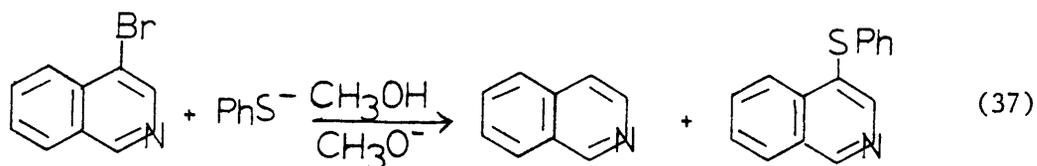
nucleophilic substitution over that of pyridine. With quinoline the most reactive position for nucleophilic attack is the 4-position and slightly less reactive is the 2-position. The 3-position of quinoline bears the same relative reactivity as does the 3-position of pyridine. In isoquinoline the most reactive site is the 1-position (note the unusual numbering system). The 3-position is much less prone to attack, although both 1- and 3-positions are α to the ring nitrogen. In both systems the ring-nitrogen does not appreciably activate a halogen in the annelated ring.

The $S_{RN}1$ reaction is strongly supported in both quinoline and isoquinoline cases. Wolfe's group has published the work concerning the 2-chloroquinoline case, and it has been found that photostimulation is a requirement for good reaction.⁵⁹ The nucleophiles examined were a set of representative ketones enolates (eq. 36).⁵⁹ It was found that the quinolyl radicals produced by the reaction show a



preference for tertiary versus primary enolates generated under competitive conditions, unlike phenyl radicals under similar reaction environments. Also, the potassium salts seemed to be the best enolates to use, except for one remarkable exception, dianions of β diketones. In such cases the lithium salts were found to be reactive enough to give good yields of substitution product in the dark. Surprisingly, the potassium salt did not react as well as the lithium salts under those conditions.

Isoquinoline has also shown $S_{RN}1$ activity. 4-Bromoisoquinoline can be made to react with benzenethiolate ion to give 4-phenylthioisoquinoline (eq. 37).⁶⁰ Addition of methoxide stimulated the



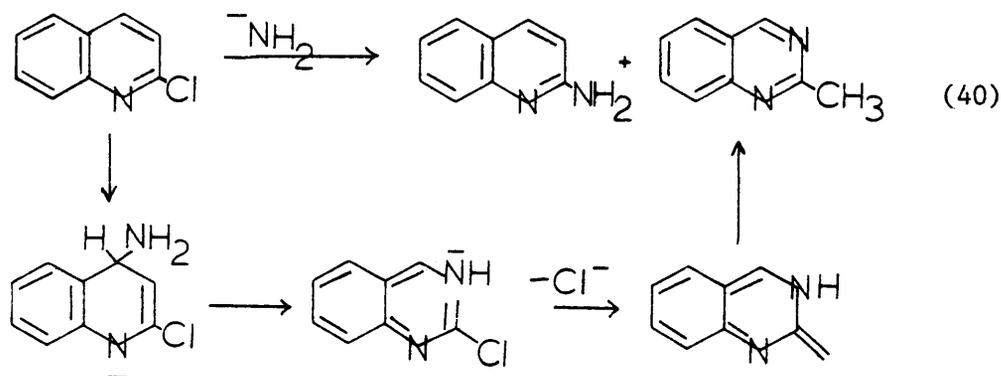
reaction and azobenzene retarded the reaction in the presence of methoxide. These results are interpreted by assuming the substitution takes place by a slow $S_{N}AR$ route in the absence of methoxide, and in the presence of methoxide the product is formed predominately via a $S_{RN}1$ type pathway. The presence of methoxide may lengthen the radical chain in the substitution process, thereby

speeding the reaction towards completion. Alternatively or in addition, the methoxide may stimulate the reaction by initiating the reduction of the aromatic halide to the radical anion. Once the isoquinolyl radical is formed, it may abstract a hydrogen atom from a suitable donor, such as methoxide (eq. 38). However, the



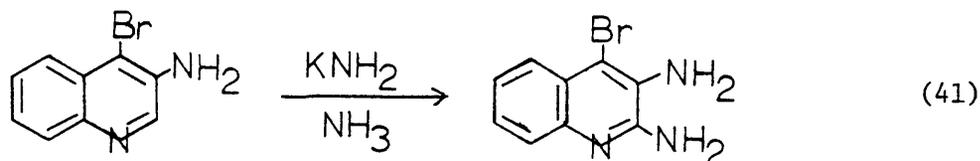
formaldehyde radical anion generated is a good electron donor and may reduce the aromatic halide to keep the chain process propagated (eq. 39). The greater nucleophilicity of the benzenethioate ion is demonstrated by only traces of methoxide substitution product being found in the reaction.

The $\text{S}_{\text{N}}\text{ANRORC}$ mechanism is found with both quinoline and isoquinoline ring systems. 2-Chloroquinoline reacts with potassium amide in ammonia to give 2-methylquinazoline and 2-aminoquinoline, the former arising from the $\text{S}_{\text{N}}\text{ANRORC}$ pathway (eq. 40).⁶¹



1- and 3-Bromoisoquinolines with KNH_2 in NH_3 were also investigated for reaction via a ring-opening process.⁶² Both compounds give the expected substitution in excellent yields. The 3-bromoisoquinoline substitution proceeds in a 55/45 ratio of $\text{S}_{\text{N}}\text{ANRORC}/\text{S}_{\text{N}}\text{AR}$; whereas 1-bromoisoquinoline seems to go exclusively via a $\text{S}_{\text{N}}\text{AR}$ path.

Formation of the σ -complex of quinoline and amide ion is known to occur.⁶³ but formation of the hetaryne appears to compete favourably in reaction of haloquinolines.⁶⁴ Amide ion can add to form a cine substitution product when blockage of the 3-position prevents hetaryne formation (eq. 41).⁶⁵ The reactivity of the



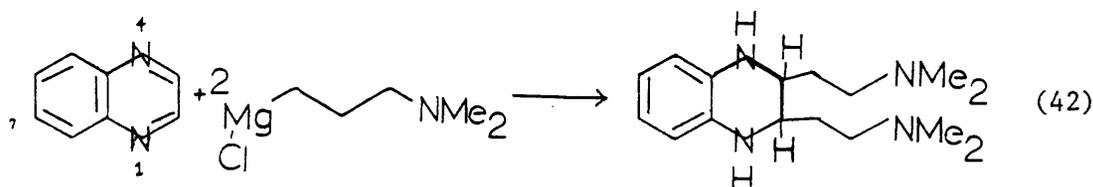
various substituted quinolynes were compared to those of benzyne, naphthalynes, phenanthryne, and pyridyne.⁶⁶ The general conclusions were replacements of a C-H by a nitrogen atom lowered the reactivity of the aryne bond.

Carbon nucleophiles including Wittig reagents displace the halogen in 1-chloroisoquinoline,⁶⁷ as does a Wittig reagent in reaction with 2- or 4-chloroquinoline.⁶⁸

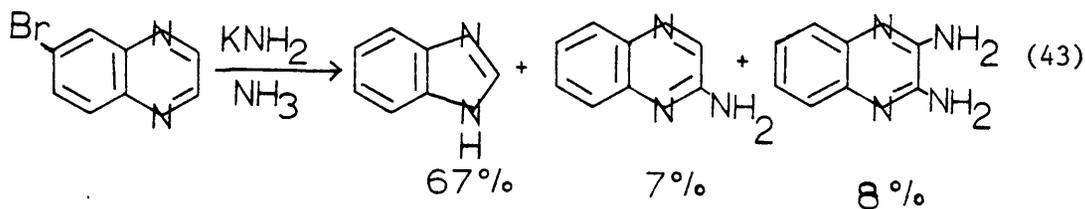
G. Quinoxaline Substitutions

Extensive reviews of quinoxalines are available,⁶⁹ and as would be expected a fair number of nucleophilic substitutions have been investigated. Interest in the quinoxaline series stems from a variety of reasons, not the least of which is the comparative ease with which they can be prepared. Also, antibiotics of the triostin and quinomycin series have been shown to be quinoxaline-2-carboxylic acid derivatives.

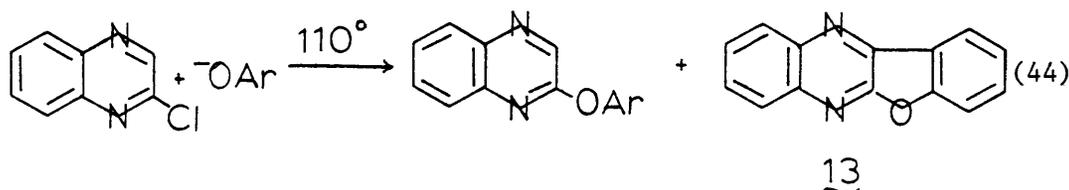
The additional activational influence of the fusion of the phenyl ring onto pyrazine is manifest in the nucleophilic substitutions of quinoxalines. Two equivalents of Grignard reagent can be added to quinoxaline (eq. 42).⁷⁰



6-Bromoquinoxaline with KNH₂ in NH₃ gives a ring contraction product, benzimidazole as well as 2-amino and 2,3-diaminoquinoxaline (eq. 43).⁷¹ Under the same conditions 2-bromoquinoxaline gives benzimidazole also.⁷²

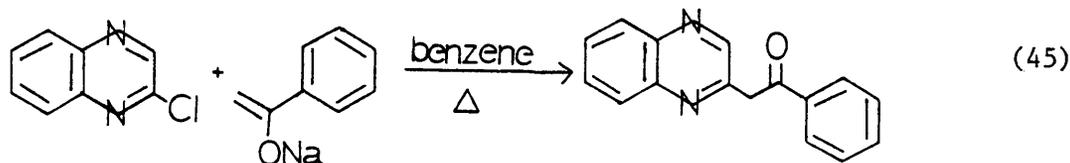


2-Chloroquinoxaline undergoes nucleophilic displacements with amines⁷³ and aryloxides.⁷⁴ Reaction of 2-chloroquinoxaline with a sodium aryloxide in an excess of the corresponding phenol gives a mixture of the substitution product and the benzofuroquinoxaline, 13 (eq. 44).⁷⁴



In this case it was found that when the initially formed quinoxyl ether was isolated, it could not be cyclized to the furan product under the reaction conditions. The 2-aryloxyquinoxalines could be cyclized by treatment with polyphosphoric acid at 140-160° C, much more strigent conditions than the reaction conditions employed above. From this evidence, the authors decided that the furoquinoxalines arose from initial nucleophilic attack of the phenoxide on the 3-position of chloroquinoxaline. This addition could conceivably be either C or O attack with subsequent displacement of the nucleofuge to give the furan.

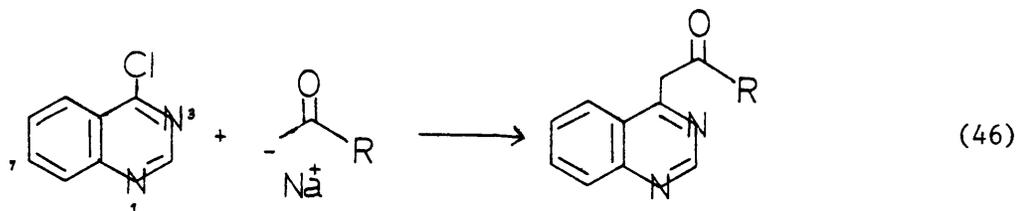
Reaction of 2-chloro- and 2,3-dichloroquinoxalines with enolate anions give 2-quinoxalinylnketones and 3-chloro-2-quinoxalinyln ketones, respectively (eq. 45).⁷⁵



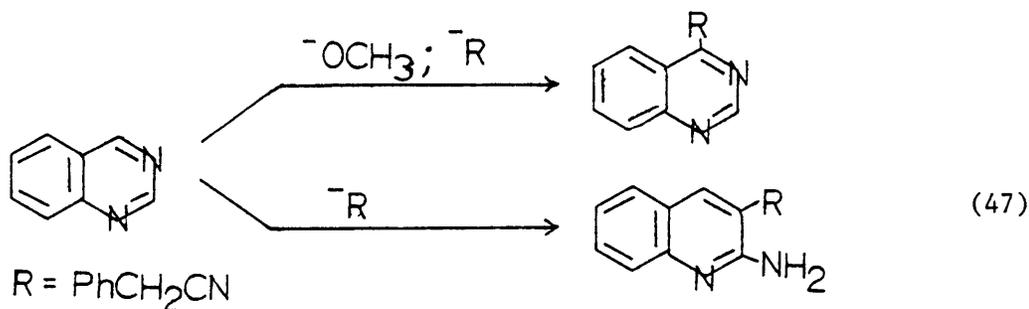
H. Quinazoline Substitutions

Because of the effect of the annelated phenyl ring onto the pyrimidine ring, the reactivity of both the 2- and 4-haloquinazolines is enhanced over that of the halopyrimidines. The reactivity of the 4-chloroquinazoline is so high that it will react spontaneously with methanol to give 4-methoxyquinazoline hydrochloride.⁷⁶ It must be noted that the 4-chlorine atom reacts 6400 times as fast as the 2-chlorine atom, and the effect of annelation in 4-chloroquinazoline, as compared with 4-chloropyrimidine, is to increase the reactivity about 100-fold.⁷⁷

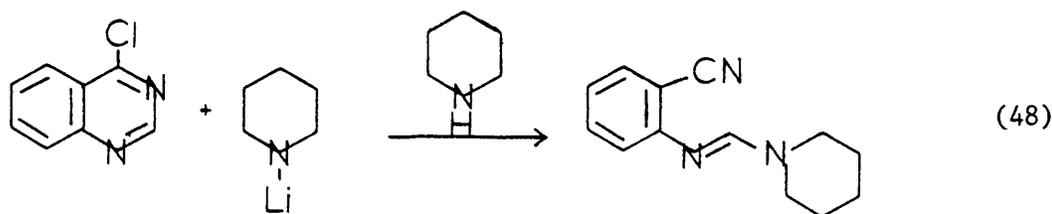
Several ketones in the presence of NaNH_2 in benzene replace the halogen of 4-chloroquinazoline to give the corresponding 4-acylmethylquinazolines in poor to fair yields (eq. 46).⁷⁸



The reactivity of the 3,4-double bond in quinazoline towards nucleophiles was illustrated by the reactions of phenylacetonitrile, nitromethane, and ethyl cyanoacetate in the presence of methoxide ions. These conditions yielded the corresponding substitution products in each case along with some 4,4'-biquinazoliny1. In the absence of the methoxide the reactions took a different course and 2-aminoquinoline derivatives were formed (eq. 47).⁷⁹ Further discussion of this reaction has been published.⁸⁰

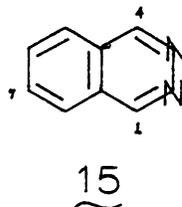
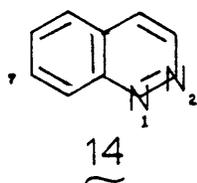


The $S_N\text{ANRORC}$ was shown to be operational in reaction of 4-chloroquinazoline with KNH_2 in NH_3 ; 50% of the 4-aminoquinazoline obtained was shown to have formed via an addition - ring-opening - ring-closing reaction.⁸¹ The remainder of the substitution product probably results from an $S_N\text{AR}$ pathway. When the reaction is performed with lithium piperidide in piperidine, the ring-opened material resulting from nucleophilic addition to the 2-position was isolated (eq. 48).⁸¹



I. Cinnoline and Phthalazine Substitutions

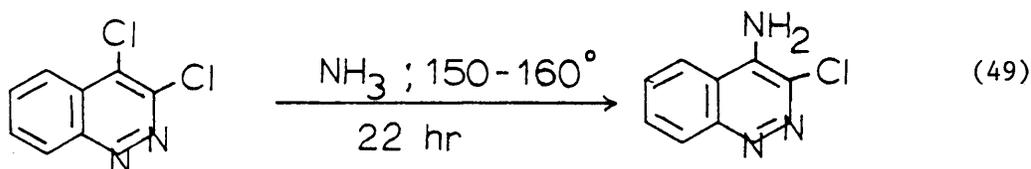
As would be expected the annelation of the benzene ring onto the pyridazine nucleus increases the reactivity of cinnoline (14) and phthalazine (15) towards nucleophilic substitution relative to the monocyclic azines. In the case of halogens attached to the



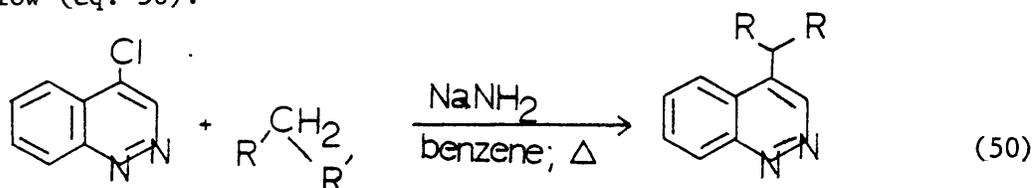
benzo portion of the heterocycle, little difference in reactivity is observed over slightly activated benzene derivatives. Nucleofuges attached to the pyridazine portion are highly activated towards substitution in both aromatic systems.⁸²

4-Chlorocinnoline, for example, reacts with boiling water to give 4-hydroxycinnoline.⁸³ Amines react easily with the 4-substituted cinnoline at conditions around 100-120° in hydroxylic solvents.⁸⁴

The halogen at the 3-position of cinnoline is much less reactive towards nucleophilic displacement than the halogen at the 4-position. This is illustrated by the following reaction (eq. 49).⁸⁵



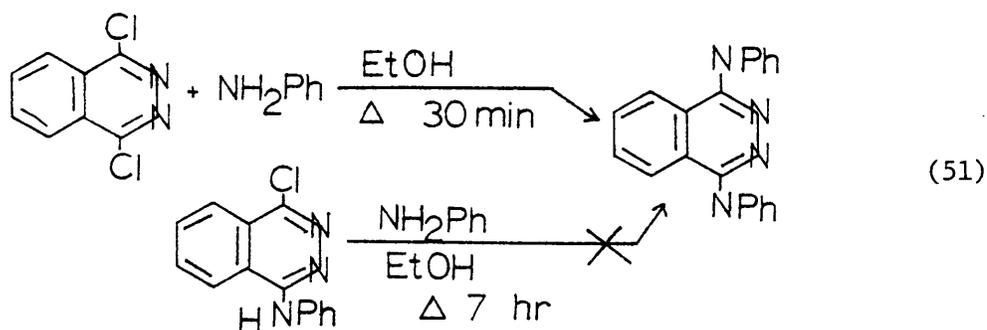
In reactions with carbon nucleophiles it was found that 4-chloroquinazoline reacts much more readily than 4-chlorocinnoline (see Section III). However, significant differences in reactivity are found between 4-chlorocinnoline and 1-chlorophthalazine with these carbon nucleophiles.⁸⁶ This can be contrasted to small differences found with oxygen and nitrogen nucleophiles reacting with these substrates.⁸⁷ An example of these reactions is given below (eq. 50).



When R = Ph and R' = CN substitution occurred readily in good yield (81%).⁸⁸

Nucleophilic substitution of the chlorine atom in 1-chlorophthalazine with nitrogen nucleophiles takes place readily. 1-Chlorophthalazine was in turn found to be more reactive than 2-chloroquinazoline, 1-chloroisoquinoline, and 2-chloroquinoline.⁸⁶ Reaction of 1,4-dichlorophthalazine with ammonia or alkylamine normally leads to monosubstitution to form 1-chloro-4-substituted phthalazines,⁸⁹ but weaker nucleophiles such as aromatic amines lead to disubstituted products (1,4-bis-diarylamino)phthalazines.⁹⁰

The reaction of 1,4-dichlorophthalazine with the weakly basic amine, aniline, proceeded smoothly in ethanol to give 1,4-dianilino-phthalazine in 58% yield after 30 min (eq. 51).⁹⁰ Reaction of



1-anilino-4-chlorophthalazine with aniline for 7 hrs in refluxing ethanol produced very little of the disubstituted product. In this case aniline hydrochloride produced by the reaction of the dichloro compound may have a catalytic effect upon the reaction. However, Kautsky and Kaiser have isolated the disubstitution product in 77% yield by refluxing 1,4-dichlorophthalazine with aniline in ether containing sodium carbonate.⁹¹

Various active methylene compounds have been used to replace the chlorine in 1-chlorophthalazine. The compounds used were benzyl cyanide, ethyl cyanoacetate, diethyl malonate, and malononitrile.⁸⁶ High yields were obtained (>65%) by using sodium amide as base and benzene as the solvent.

III. Relative Reactivities of Aromatic Diazines

The relative reactivities of the aromatic diazines has been studied from the standpoint of nucleophilic substitution. Excellent reviews are available that compile available literature data for these aromatic heterocycles.⁹² One study on the reactivities of chloro-derivatives of various heterocycles is given in Table I.⁸⁷

Other workers have reported rate data for trimethylammonium derivatives of the heterocycles (Table II).^{93a,b} Table II is not complete since phthalazines, cinnolines, pyrazine, and pyridazines are missing due to the inability of the authors to obtain the trimethylammonium compounds by the procedures used. However, in the salts that were able to be isolated, the results in Table II indicate that the ammonium salts activate the ring towards substitution much more than halogen substituents. Activating effects of the trimethylammonium group was about 3000 times greater than those of halogen substituents.

Illuminati has studied the kinetics of methoxide substitution on a variety of aromatics, and some of the results are listed in Table III.⁹⁴

Table I

Relative Rates of Reactions of Heteroaromatics

Substrate in S_NAR Substitutions

| | Rate of Reaction at 20° C | |
|----------------------|---------------------------|-------------------------|
| | Ethoxide ion | Piperidine |
| 3-chloroisoquinoline | 1.2 x 10 ⁻⁹ | - |
| 2-chloropyridine | 2.2 x 10 ⁻⁹ | 2 x 10 ⁻¹⁰ |
| 4-chloropyridine | 8.7 x 10 ⁻⁸ | - |
| 2-chloroquinoline | 6.3 x 10 ⁻⁷ | 1.5 x 10 ⁻⁷ |
| 4-chloroquinoline | 6.5 x 10 ⁻⁷ | - |
| 1-chloroisoquinoline | 6.9 x 10 ⁻⁷ | 2.5 x 10 ⁻⁷ |
| 2-chloropyrimidine | 1.7 x 10 ⁻³ | 3.0 x 10 ⁻⁴ |
| 1-chlorophthalazine | 1.9 x 10 ⁻³ | 2.0 x 10 ⁻⁵ |
| 2-chloroquinazoline | 3.0 x 10 ⁻³ | 4.3 x 10 ⁻⁴ |
| 4-chlorocinnoline | 4.8 x 10 ⁻³ | - |
| 2-chloroquinoxaline | 8.32 x 10 ⁻³ | 6.2 x 10 ⁻⁵ |
| 4-chloropyrimidine | - | 1.58 x 10 ⁻³ |
| 4-chloroquinazoline | - | 3.1 |

Ref. 87

Table II

Reaction of Trimethylammonium Heterocycle Derivatives
With Hydroxide

| Substrate | T ° C | Rate Constant in 1 mol ⁻¹ sec ⁻¹ |
|--|--------|---|
| 2-pyridyltrimethylammonium iodide | 20° | 8 x 10 ⁻⁹ |
| quinolin-2-yltrimethylammonium iodide | 20° | 8.6 x 10 ⁻⁶ |
| 2-chloropyrimidine | 20° | 7.9 x 10 ⁻⁵ |
| 4-chloroquinazoline | 19.85° | 5.88 x 10 ⁻³ |
| pyrimidin-2-yltrimethylammonium chloride | 20° | 5.75 x 10 ⁻² |
| pyrimidin-4-yltrimethylammonium chloride | 20° | 1.62 x 10 ⁻¹ |
| quinazolin-2-yltrimethylammonium chloride | 20.2° | 2.89 x 10 ⁻¹ |
| 2-methylsulphonylpyrimidine | 20° | 3.01 x 10 ⁻¹ |
| quinazolin-4-yltrimethylammonium chloride | 20.4° | 4.29 |

Ref. 93

Table III

Rate Constants for Nucleophilic Substitution With
Methoxide on Various Aromatics

| Substrate | T° C | $10^6 \cdot k(1 \text{ mol}^{-1} \text{ sec}^{-1})$ |
|-----------------------------|------|---|
| 2-chloroquinoxaline | -10 | 213 |
| 2-chloroquinoline | 99.5 | 1940 |
| 4-chloronitrobenzene | 99.5 | 1260 |
| 2-chloronitrobenzene | 99.5 | 339 |
| 2-chloro-4-methoxyquinoline | 99.5 | 321 |
| 4-chloro-2-methoxyquinoline | 99.5 | 121 |
| 2-chloropyridine | 99.5 | 17.9 |

Ref. 94

From the data in Tables I-III, we can draw a relative reactivity sequence for nucleophilic substitution in these heteroaromatics. However, pyridazine and pyrazine are missing from these tables. Comparative studies in the literature help place the various halo-derivatives of these heterocycles into a reactivity scale. Barlin and Brown have noted that the methylsulfonyl derivatives of pyrazine and pyridazine are more reactive than the corresponding chloro groups in reaction with methoxide.⁹⁵ The observed order of reactivity in this case was 4-substituted pyridazine > 3-substituted pyridazine > 2-substituted pyrazine.

To place this order of reactivity into relationship with the other heterocycles, results obtained by Miller help complete the picture. The chloro derivatives of pyrimidine, pyridazine, and pyrazine show different reactivities with p-nitrophenol anion.⁹⁶ This study places 2-chloropyrimidine > 4-chloropyrimidine > 4-chloropyridazine \approx 3-chloropyridazine > 2-chloropyrazine. The reactivity order is unusual in that the 2-chloropyrimidine is placed higher than the 4-chloropyrimidine; more common is the opposite ranking.

Using this data to construct a listing of S_NAR reactivities of these heterocycles can be compiled, but it is not rigorously followed by all nucleophiles in all solvents. Despite its obvious limitations, it will be helpful in the following discussions to have some idea of the various propensities these heterocycles usually display toward nucleophilic substitution reactions (Table IV).

Table IV

Listing of S_NAR Activities of Various Chloroderivatives
of Heterocycles

4-Chloroquinazoline

4-Chloropyrimidine

2-Chloroquinoxaline

4-Chlorocinnoline

2-Chloroquinazoline

1-Chlorophthalazine

2-Chloropyrimidine

4-Chloropyridazine

3-Chloropyridazine . .

2-Chloropyrazine

1-Chloroisoquinoline

4-Chloroquinoline

2-Chloroquinoline

4-Chloropyridine

2-Chloropyridine

3-Chloroisoquinoline

3-Chloropyridine

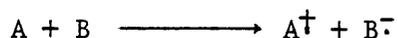


Increasing
Reactivity

IV. Investigation of the S_{RN}1 Mechanism in Nitrogen Heterocycles

From the preceding sections it is clear that there are many unsolved problems in nucleophilic aromatic substitution. Recently the possibilities of electron transfer have been considered in aromatic substitutions, and these processes have been found to play a large role in many of these reactions.⁹⁷ Theoretical studies on the one-electron transfer reaction have focused on the oxidation-reduction process that constitutes the first step of an electron transfer mechanism, such as found in the S_{RN}1 reaction. These studies have not restricted their models to nucleophilic substitution but have also considered electrophilic attacks on aromatics.

Investigators have examined these substitution reactions from the standpoint of oxidation-reduction processes, and this is a valid concept as long as a few limitations are remembered. For example, in the red-ox equation below, comparison of the oxidation potential



of A to the reduction potential of B should give a number that would be useful for predictive purposes in reactions with similar solvation energy. However, the following points must be considered:

- 1) The reduction potentials obtained for species A and B must be true thermodynamic values (i.e., those indicated by reversible cyclic voltametry)
- 2) The activation energies must be related to the thermodynamic values in (1)
- 3) The reaction must proceed by the electron transfer mechanism.

Consideration of the above points can lead to good theoretical descriptions and predictions.⁹⁹ Generalized Hartree-Fock (GHF) calculations^{98,100} indicate that nucleophilic aromatic substitutions may be classified into three types: 1) nonradical ionic (i.e., S_NAR , AE, EA, etc.); 2) electron-transfer type I (ET I); 3) electron-transfer type II (ET II). The nonradical process is the typical two-electron addition to the aromatic molecule (formation of the σ -complex) with concurrent bond formation between the two species. In the ETI process there is electron-transfer between the two species, but this occurs at an intermediate stage of the reaction where there is partial bond formation between the reactants. ET II, on the other hand, produces an electron-transfer at an initial stage of the reaction when there is little bond formation between the species.

Using GHF calculations and very simple models, the observation was made that with some nucleophiles (and electrophiles) there is a considerable amount of electron transfer occurring between the reagents and the aromatic molecule. For example, with NO_2^+ there is a large amount of the ET character at a relatively short intermolecular distance (2.0 Å) between the reaction sites, and the bond order is comparatively large (.45). This is classified as an ET I reaction. With hydride as a nucleophile it is found that a large amount of charge transfer takes place at a longer intermolecular distance (2.5 Å); however, the bond order between the reaction sites

is very small. In this case the dissociation of the radical pair into two radicals may be possible if the solvation energy exceeds the interaction energy of the pair. This is classified as an ET II reaction.

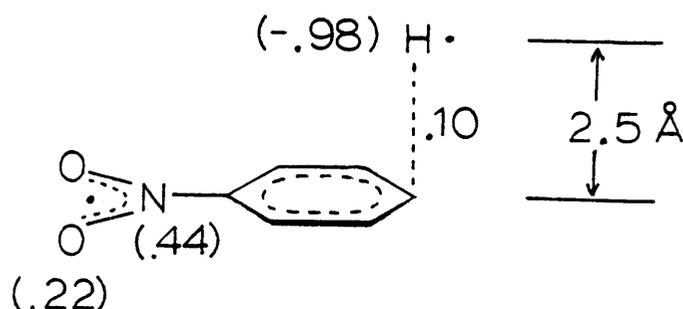


Diagram 1. Bond Order and Spin Density (in parentheses) of H^{\bullet} Attacking Nitrobenzene (ET II)

Presumably in cases where the transition states have large amounts of charge transfer, and solvation energies can compete with binding energies, electron transfer processes such as the $S_{RN}1$ can take place.

Comparison of the LUMO of the aromatic to the HOMO of the nucleophile should in a semi-quantitative way give us a relative reactivity scale.¹⁰¹ A good measure of these orbitals are the electrode reduction potentials.¹⁰² Comparison of the oxidation and reduction potentials is valid, if "things being equal" include the solvation energy ($\Delta\Delta G_{SOL}$) and transition state energy as governed by charge transfer complex formation are the same or tend to cancel each

other. With this assumption the thermodynamic value obtained from an electrochemical reduction can be expected to give a prediction of the relative kinetics of a $S_{RN}1$ substitution reaction. In other words, the nature of the transition state of the initiation step is, at least partially, product controlled, and the other steps of the $S_{RN}1$ mechanism are similar for most aromatic substrates and nucleophiles.

The existence of the "thermodynamic" $E_{1/2}$ potential correlation described above requires the redox system to be simple, rapid, and reversible. Also, these conditions must hold for the entire series of compounds which exhibit no changes in solvation energies.¹⁰² It is surprising that so many satisfactory correlations have been made; for these restrictions seem to be very limiting. Certainly there must be some kind of cancelling of errors in these cases.

With these parameters remaining virtually static and the transition state of the electron transfer step being product controlled, we can expect that decreasing the energy of the LUMO in the electron acceptor (such as the aromatic halide), should lead to a greater number of initiations per unit time. In a chain reaction increasing the number of initiations per unit time leads to increased rates. Also, increasing the energy of the HOMO of the electron donor would facilitate the electron transfer to the acceptor in this type of situation.

After the initial electron-transfer has taken place, we would expect the decomposition of the radical anion into the aromatic radical and halide anion to proceed smoothly.¹⁰³ In most cases this is true. However, examples in which this reaction does not occur readily are known. We should consider the reduction potential and the strength of the carbon-halogen bond to be an approximation for the energy available for fragmentation.

Fluoride is not expelled from the radical ion of fluorobenzonitrile or fluoropyridine.^{31,120} Other examples include those of Grimshaw and coworkers, who demonstrated that both the reduction potential of the halogenated aromatic and the free electron density at the carbon site holding the nucleofuge played a role in the rate of decomposition of certain aromatic radical anions.^{104b} They found the 4-isomer of chlorostyrylpyridine reacts rapidly at the electrode to reduce and fragment at a rate estimated at $k = 1.5 \text{ s}^{-1}$. The 3-isomer, on the other hand, gives $k = 6.9 \times 10^{-2} \text{ s}^{-1}$. Comparison of the free electron densities at C-4 and C-3 is .085 and .004, respectively. This points to the electron density at the carbon bearing the nucleofuge as being a factor in the rate of decomposition of the radical anion.

Hawley¹⁰⁵ used an argument based on steric effects to explain the rapid decomposition of 2-iodonitrobenzene vs. those of the meta- and para-isomers. However, rate variation between these isomers can be rationalized in terms of free electron density on the carbon atom involved in the fragmentation.^{104b}

Summarizing the trends expected for haloaromatic radical anion decompositions, the following points should be considered as possible factors:

- 1) increasing the halogen bond strength decreases the rate of fragmentation (Chloro-substituted radical anions are stable when the $E_{1/2}$ value for the parent system is less negative than -1.6V vs SCE and bromo-derivatives when $E_{1/2}$ -1.2 to 1.6 V vs SCE. Iodo-derivatives are estimated to be stable only at less negative value than 1.1 V vs SCE)^{104b}
- 2) unusually low free electron density on the carbon site can slow the rate of decomposition
- 3) more negative reduction potentials necessary for radical anion formation increase the rate of disassociation
- 4) steric compression seems to increase the decomposition rate.

The factor mentioned in 2) must be amended somewhat. The free electron density in the parent molecule radical anion is only an approximation of the charge density distribution in the halo-substituted radical anion since the halogen p orbital can overlap with the aromatic π -orbitals to perturb the radical anion to a different electron distribution from that of the parent radical anion. However, good correlations with several different systems have been made.^{104b,106,107,108} These observed trends hold since the parent aromatic whose spin densities were measured, have electronic distributions similar to the aromatic containing the nucleofuge (ionogenic group).

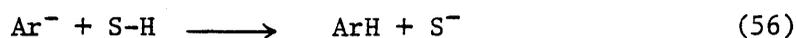
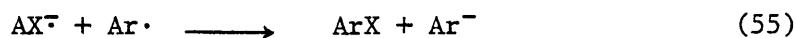
At this point, it should be mentioned that the ESR spectrum of the radical ion is the best experimental method available for determining the electron spin densities on the various carbon atoms. Determination of the hyperfine interaction constant for the i^{th} hydrogen atom gives a constant, a_i^{H} . This constant is directly proportional to the spin density of the i^{th} carbon atom to which the i^{th} hydrogen is bonded.¹⁰⁹ The relationship that results is commonly called the McConnell equation:

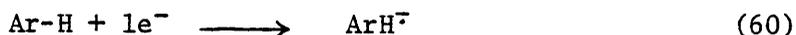
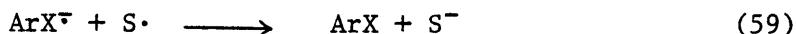
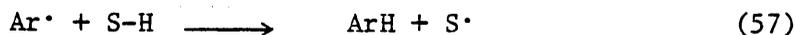
$$a_i^{\text{H}} = Q_{\text{CH}}^{\text{H}} \rho_i^{\pi}$$

Here Q_{CH}^{H} is the proton hyperfine splitting for a unit spin density in a π -orbital and ρ_i^{π} is the spin density on the measured carbon atom.

Determinations of this kind require that the anion radical have a long enough life-time so that an appreciable concentration of the species can build to the point where a suitable ESR spectrum can be obtained.

Radical anions of haloaromatics are often short-lived owing to the following series of reactions.

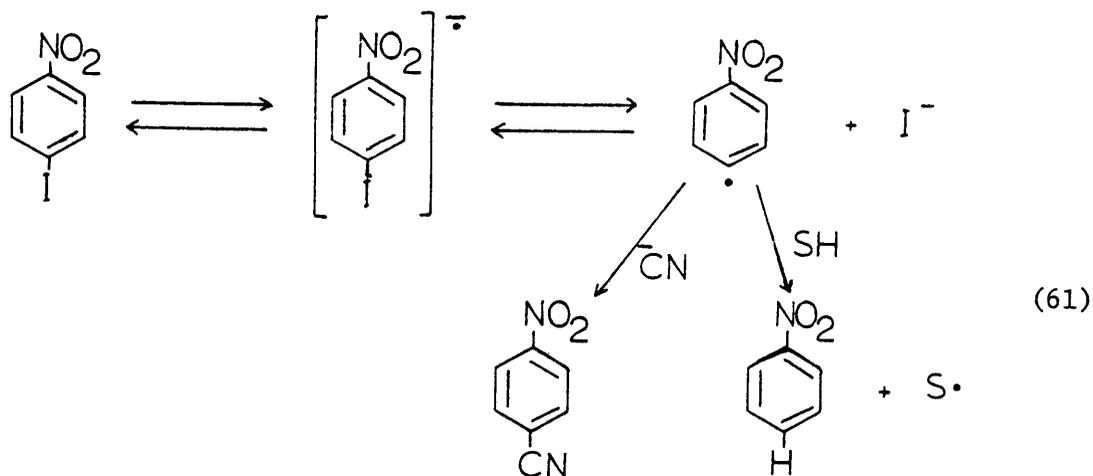




If the radical ions are generated by electrochemical means in nonaqueous solvents,¹¹⁰ several processes detailed in the above equations occur rapidly. The radical ion formed in eq. 53 fragments to the neutral radical ($k_{1\text{st order}} > 10^4 \text{ s}^{-1}$).^{110a} The radical may then undergo further reduction at the electrode surface (eq. 54) or abstract a hydrogen from the solvent media (eq. 57). The ArH formed by either of these two processes may be further reduced to the radical anion (eq. 60). Thus, the ESR signal that would be seen might not necessarily be the radical anion of the halogenated aromatic.

The lifetime of the halogenated radical anion is a factor which determines whether the reduction or ArH takes place by hydrogen atom abstraction from the solvent or by the electrode reduction. If the lifetime of the radical anion is sufficient to allow the species to diffuse from the electrode surface into the bulk of solution, the radical is reduced by the solvent hydrogen abstraction route (eq. 57).¹¹¹

Once the radical is formed, by whatever process, in order to continue the chain reaction towards overall substitution, it must combine with an anion. The literature is abound with examples of this type process. A good example is that of Hawley¹¹² who noted that electrochemical reduction of p-iodonitrobenzene in the presence of cyanide anion led to a mixture of the reduced aromatic and the substituted nitrobenzene (eq. 61). That a radical will combine with



an anion is not unreasonable, since only bond-formation and no bond-cleavage processes are involved.

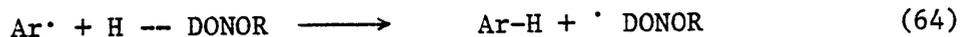
We wonder at what point will the combination of radical and nucleophile no longer be favorable. Obviously, there is some limit that is clearly dependent upon the stability of the nucleophile, since the stable bases such as bromide and chloride ions do not favor combination. It is surprising that a weak base such as cyanide can be induced to couple with the radical. The increased stabilization of the radical anion of the product by the nitrile function may play a large role in preventing the reverse of the combination from taking place. Other weak bases such as the monoenolate of β -diketones have been suspected of being unable to combine with the phenyl radical.¹¹³ However, other possibilities have not been ruled out in these cases.

One factor in the combination of the aromatic radical and carbanion that should be considered, is equilibrations of the type written in eq. 62.



If equilibrations of this type are important, then product ratios will reflect thermodynamic factors that influence the stability of the radical anion of the substitution product. Since it is likely that the electron transfer in eq. 63 is essentially irreversible (because ArX^- decomposes), once electron transfer from ArNu^- takes place, further equilibration is halted in this radical anion. Therefore, we would expect two factors to be important in equilibrations of this type, 1) the stability of Ar^\cdot and Nu^- relative to ArNu^- and 2) the rate of electron transfer from ArNu^- to ArX (eq. 63).

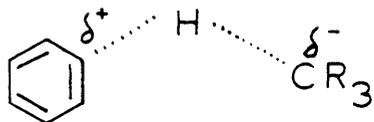
Other reaction paths that are available for the radical include hydrogen atom abstraction from the solvent or other species that may be present in the reaction (eq. 64). This reaction has been found



to be the predominant mode of reduction of iodobenzene in reaction with diisopropylketone enolate.¹¹⁴ Abstraction of hydrogen from the diisopropylketone enolate is thought to be a particularly facile process due to the stability of the hydrogen-atom abstracted enolate 16, which is the radical anion of an α, β -unsaturated ketone (eq. 65). To explain the anomalous slow reaction with these particular substrates, a chain terminating progression of events was postulated as written above. Other more reasonable explanations for the fate of

In the heteroaromatic case, pyridine and quinoline have been shown not to suffer as much reduction as their phenyl analogs. A variety of explanations can be put forth, but the interpretation suggested in the literature is that due to the differing nature of the aromatic radicals, the rates of enolate combination differ as well as hydrogen abstraction rates. For example, in competitive experiments both the 2-quinolinyl and 2-pyridyl radicals favored combination at tertiary enolate over primary enolate sites. This indicates that these heterocyclic radicals have a degree of selectivity in their combinations. Phenyl radicals, on the other hand, show little preference for tertiary enolates, and this implies that it is a less stable radical.¹¹⁵

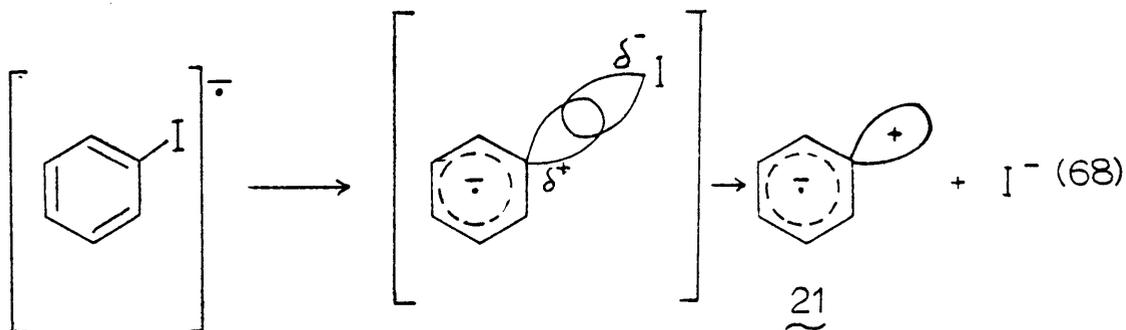
Generally, radicals are viewed as being electron deficient species, and the initial formulation of a π -deficient heteroaromatic radical is to view it as being more electron deficient than an analogous phenyl case. This would then make the radical more unstable (higher energy), and imply that in its reactions it would be less selective. However, the published results seem to point to the fact that the heteroaromatic radicals are more stable and more electrophilic. A published report¹¹⁶ indicates that the transition state of hydrogen abstraction by phenyl radicals has a polarized transition state with substantial positive charge build-up on the attacking phenyl radical. In this case increasing the electron-deficiency of the radical would intensify the positive charge build-up

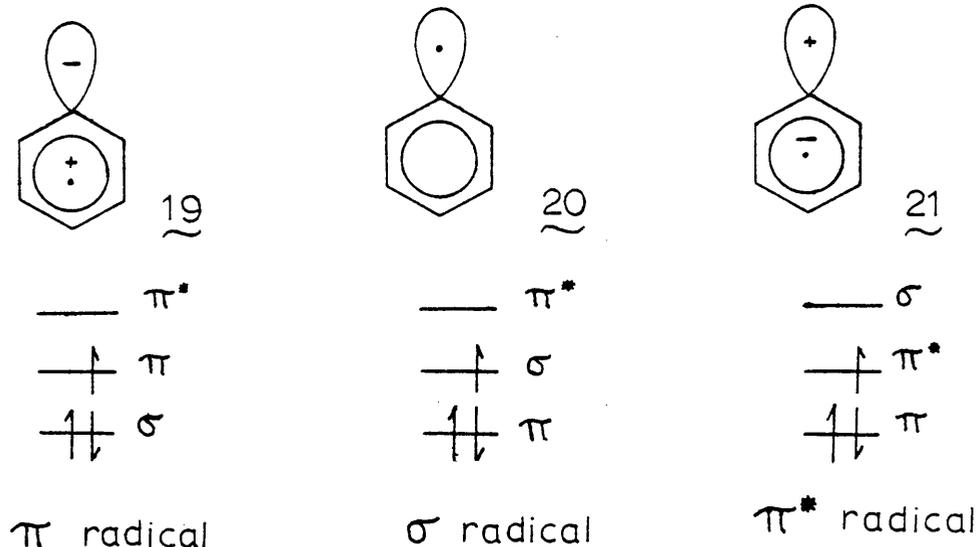


on the aromatic radical and destabilize the transition state. If the radicals are more stable, the tendency for hydrogen abstraction may be reduced.

Also, the hydrogen abstraction route may be less important in heteroaromatics just because the rate of anion and radical coupling is increased in rate. This would decrease the amount of hydrogen abstraction products since anions efficiently scavenging heteroaromatic radicals as they are formed would reduce the concentration of these radicals. This reactivity of heteroaromatic radicals generated in this manner can be interpreted by the following models of electronic structure.

In forming the pyridine radical, the transition state may have the character of intermediate 21 (eq. 68). This model assumes that





the breakage of the sigma bond to the nucleofuge is a heterolytic cleavage with little overlap of σ and π^* orbitals. The heterolytic cleavage would give, by a symmetry allowed process, a π^* radical. The ground state of both phenyl and pyridyl radicals have been shown to be σ -type (20).^{117,118} Therefore, the radical initially generated by radical anion decomposition is the excited state of the σ -radical. The rate at which this π^* radical degenerates into the ground state is questionable. To account for the two different types of reaction that the phenyl radical is implicated to perform, it is tempting to assign different reactivities to the different states of the radical. Presumably, the excited state as indicated by the π^* radical is more prone to combine with a nucleophile; whereas, the σ -radical would have more nucleophilic character and would be a better hydrogen atom abstractor.

In the case of the phenyl radical, the decay of the π^* radical to the σ -radical could be faster than that of an analogous π -deficient heterocycle. This would then give more of the ground state phenyl radical

to abstract hydrogens. In this connection, the decay of the excited heteroaromatic radical to its ground state could be slower than in the phenyl case, because the excited (π^*) radical is relatively more stable. In other words, the energy gap between the ground state and the excited state is less in the heterocycle's case than in the phenyl system. At first glance this would intuitively appear to be exactly opposite of the true case; however, consideration must be taken of the pyridyl cation. Calculations have shown this cation to be more stable than the phenyl.

The apparently smaller energy gap between the σ and π^* radicals in pyridine could be the cause of effective anion and radical combination. Excitation of the σ radical to this electronic state initially or along some point of the reaction coordinate could be a major portion of the activation energy required for radical and anion coupling. Once again, the smaller energy gap in pyridyl radicals between the σ and π^* forms may be responsible for very fast coupling of anion and radical.

Once the anion and the aromatic radical have coupled, the product is the radical anion of the substituted product. In benzoaromatic cases in which the nucleophile is an enolate, the ground state of this radical anion is best represented by the ketyl resonance form; whereas, with annelated benzoaromatics and heteroaromatic compounds the radical anion may best be expressed as having the extra electron localized on the aromatic portion of the product.¹¹⁹ The stability or lack of stability in this radical anion is crucial for the next step of the $S_{RN}1$ reaction.

Electron transfer from the radical anion of the product back to the aromatic substrate must be facile. Otherwise, a buildup of radical anions at this stage could lead to slow overall reaction rates. There is no evidence at this stage that conclusively points to this sequence as the cause of failure in reactions in which the $S_{RN}1$ mechanism does not take place. Conceivably, certain situations could arise in which a particularly stable radical anion could be formed that could not reduce the substrate.

Termination steps such as radical dimerizations are not extremely important, although they do put a practical limit on the chain length. The low concentration of radicals at any given time usually prevents these type of products from being easily detected upon work-up of the reaction. Therefore, their lack of detection does not provide negative evidence for the radical nature of these processes. The best evidence for radical character is the inhibition of these processes by radical scavengers.¹⁹

V. Rationale for the Present Investigation Concerning the Scope and Limitations of Heteroaromatic Nucleophilic Substitutions Occuring via a Radical-Chain ($S_{RN}1$) Mechanism

From the previous discussion of the $S_{RN}1$ mechanism involving aromatic substrates, it should be noted that this electron transfer mode of substitution has not been widely recognized as a viable mechanism in heteroaromatic nucleophilic substitutions. The aromatic systems that have been studied to date include substituted benzenes,

naphthalenes, phenanthrenes, anthracenes, thiophenes, haloisoquinolines, 2-chloroquinoline, and 2-,3-, and 4-halopyridines.²⁰ The success of these reactions indicated that the viability of this mechanism in other heteroaromatics should be investigated. The mild conditions and good yields found in most systems strongly suggested that the synthetic potential of this substitution mechanism would be excellent. In view of this, and because of the interesting mechanistic information to be gained, an investigation into the scope and limitations of this electron transfer reaction as applied to a series of halogenated heteroaromatics was initiated.

One of the objectives of this study was to determine the structural features which the halogenated heterocycles must possess in order to participate in the radical-chain process. The factors that presumably have a bearing on this reactivity are the following:

- 1) the number and position of the heteroatoms
- 2) the stability of the radical anion formed in the initiation step
- 3) the position and type of halogen.

The factor listed in 1) and 2) can be related to the reversible one-electron $E_{1/2}$ values obtained by electrochemical reduction of the parent heteroaromatic. The value of this $E_{1/2}$ potential may determine the number of initiations that take place per unit time, and in that way govern the rate of the radical-chain reaction. Conceivably, if the reduction potential occurs at too low* a cathodic

*The designation "low" refers to less negative values of $E_{1/2}$.

potential, the radical anion of the aromatic substrate may not expell the nucleofuge. This unimolecular decomposition may then become the rate determining step in the overall reaction. Also, the free electron density on the carbon bearing the nucleofuge in the radical anion may play a role in this decomposition step.

From the published reduction potentials of a series of unsubstituted heteroaromatics, it seemed likely that these heterocycles would undergo $S_{RN}1$ reactions, and they should display relative reactivities that reflect the values of their one-electron reduction potential. In other words, aromatics with "lower" (less negative) reduction potentials should undergo more facile $S_{RN}1$ type substitutions than those with "higher" (more negative) reduction potentials.

The heterocycles investigated in the present study include 2-chloropyrimidine, 4-chloro-2,6-dimethoxypyrimidine, 3-chloro-6-methoxypyridazine, 2-chloropyrazine, 4-chloroquinazolines, 2-chloroquinoxalines, and some isomeric dihalo derivatives of these heterocycles.

A representative selection of ketone enolates were used as nucleophiles to gauge the $S_{RN}1$ reactivity of these heteroaromatics. Enolates that possess hydrogens β to the carbonyl carbon were employed to assess the amount of reduction produced by hydrogen atom transfer. This has not been shown to be a major problem in heteroaromatics studied previously.^{19,20}

In cases studied to date the solvent that shows the most promise for supporting the electron transfer radical nature of the $S_{RN}1$ mechanism is liquid ammonia. For this reason, liquid ammonia was used as the reaction solvent in this study.

In order to demonstrate the radical-chain nature of the substitution reactions, a catalytic amount of di-*t*-butylnitroxide or *p*-dinitrobenzene was added to the reaction to act as an inhibitor. The chain character of the $S_{RN}1$ reaction is indicated by the almost complete inhibition of substitution product by only catalytic amounts of the inhibitor. Other pieces of evidence that point to operation of the $S_{RN}1$ mechanism include the following:

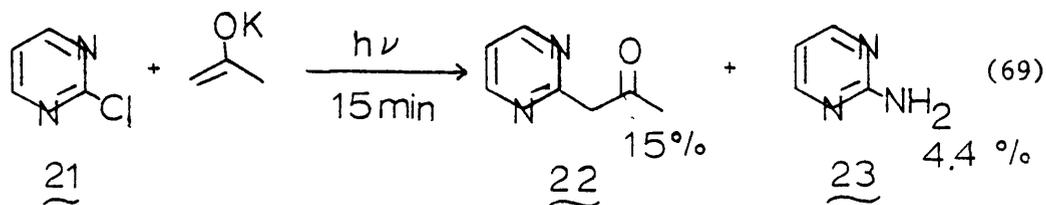
- 1) Photostimulation may be required
- 2) Stimulation by adding alkali metals
- 3) Stimulation by other routes that produce free radicals
- 4) Formation of disubstitution with no build-up of monosubstitution products in reactions with dihaloaromatics.

This investigation was designed to further define the possible operation of the radical-chain mechanism with heteroaromatic substrates. Recognition of this mechanism in these haloazines will help provide an understanding of the conditions necessary for more facile nucleophilic substitutions in aromatic heterocycles. Also, correlation of $S_{RN}1$ reactivity with the reduction potential of the heteroaromatic may provide an index for predicting the likelihood of the $S_{RN}1$ mechanism in unexplored areas.

VI. Results and Discussion

A. Pyrimidine

The initial study focused on the reaction of 2-chloropyrimidine (21) with several ketone enolates. The results of these reactions are summarized in Table V. Using conditions that had previously been found to be most favorable toward $S_{RN}1$ substitutions, that is, refluxing liquid ammonia and photostimulation, a disappointingly low (15%) yield of 1-(pyrimidin-2-yl)-2-propanone (22) along with a small amount of 2-aminopyrimidine (4.4%, 23) were obtained as the only isolable products from the reaction of potassium acetone with 21 after 15 min of irradiation (eq. 69). The remainder of the



reaction mixture was a dark red water-soluble tar. This red material darkened slowly upon exposure to air and was sparingly soluble in ethyl acetate and alcohols.

In a similar reaction, treatment of pyrimidine (21) with the potassium salt of pinacolone, under photostimulation for 15 min gave 32% of the substituted pyrimidine, 24, and a small amount of 2-aminopyrimidine (4.4%, eq. 70). However, when diisopropyl ketone enolate was used as the nucleophile, photostimulation for 15 min

Table V

Reaction of 2-Chloropyrimidine with Ketone Enolates

| Expt. No. | Ketone | Conditions ^{a,b} | Product No. | Yield |
|-----------|-----------------------|----------------------------|-------------|-------|
| 1 | acetone | hv | <u>22</u> | 15% |
| | | | <u>23</u> | 4.4% |
| 2 | acetone | dark | <u>22</u> | 0% |
| | | | <u>23</u> | 5.2% |
| 3 | acetone | hv; inhibited ^c | <u>22</u> | 0% |
| | | | <u>23</u> | 5.2% |
| 4 | pinacolone | hv | <u>24</u> | 32% |
| | | | <u>23</u> | 4% |
| 5 | diisopropyl ketone | hv | <u>25</u> | 88.5% |
| | | | <u>23</u> | 4.3% |
| | | | <u>26</u> | 1/2% |
| | | | <u>27</u> | 1/2% |
| 6 | diisopropyl ketone | dark | <u>25</u> | 0% |
| | | | <u>21</u> | 50% |
| | | | <u>23</u> | 7.5% |
| | | | <u>28</u> | 16% |
| 7 | diisopropyl ketone | hv; inhibited ^d | <u>25</u> | 0% |
| | | | <u>21</u> | 58% |
| | | | <u>23</u> | 6.8% |
| | | | <u>28</u> | 15% |

^aReaction time 15 min.

^bRatio of enolate to substrate, 3.75:1

^c10 mol% of DTBN was used as an inhibitor

^d20 mol% of DTBN was used as an inhibitor.

Table VI

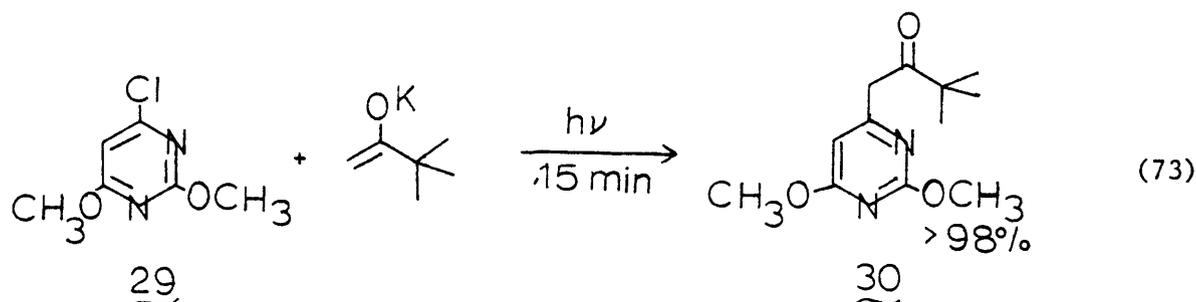
Reaction of 4-Chloro-2,6-dimethoxypyrimidine
with Ketone Enolates

| Expt. No. | Ketone | Conditions ^{a,b} | Product No. | Yield |
|-----------|------------|----------------------------|-------------|-------|
| 10 | pinacolone | hv | 29 | 1% |
| | | | 30 | 98% |
| 11 | pinacolone | dark | 29 | 80% |
| | | | 30 | 0% |
| 12 | pinacolone | hv; inhibited ^c | 29 | 65% |
| | | | 30 | 6% |

^aReaction time 15 min.

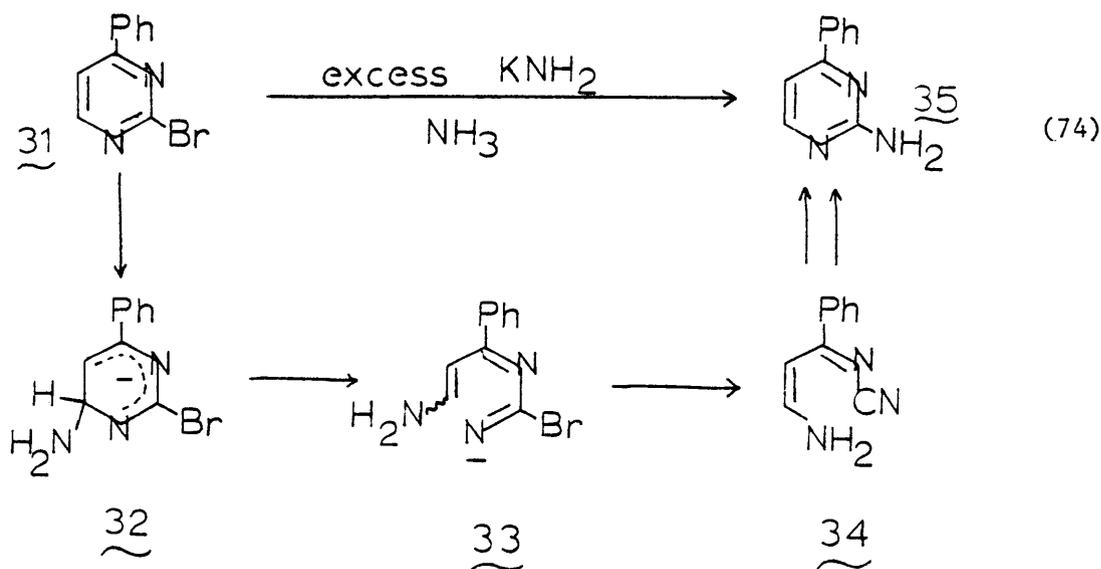
^bRatio of enolate to substrate, 3.75:1

^c20 mol % of DTBN was used as an inhibitor



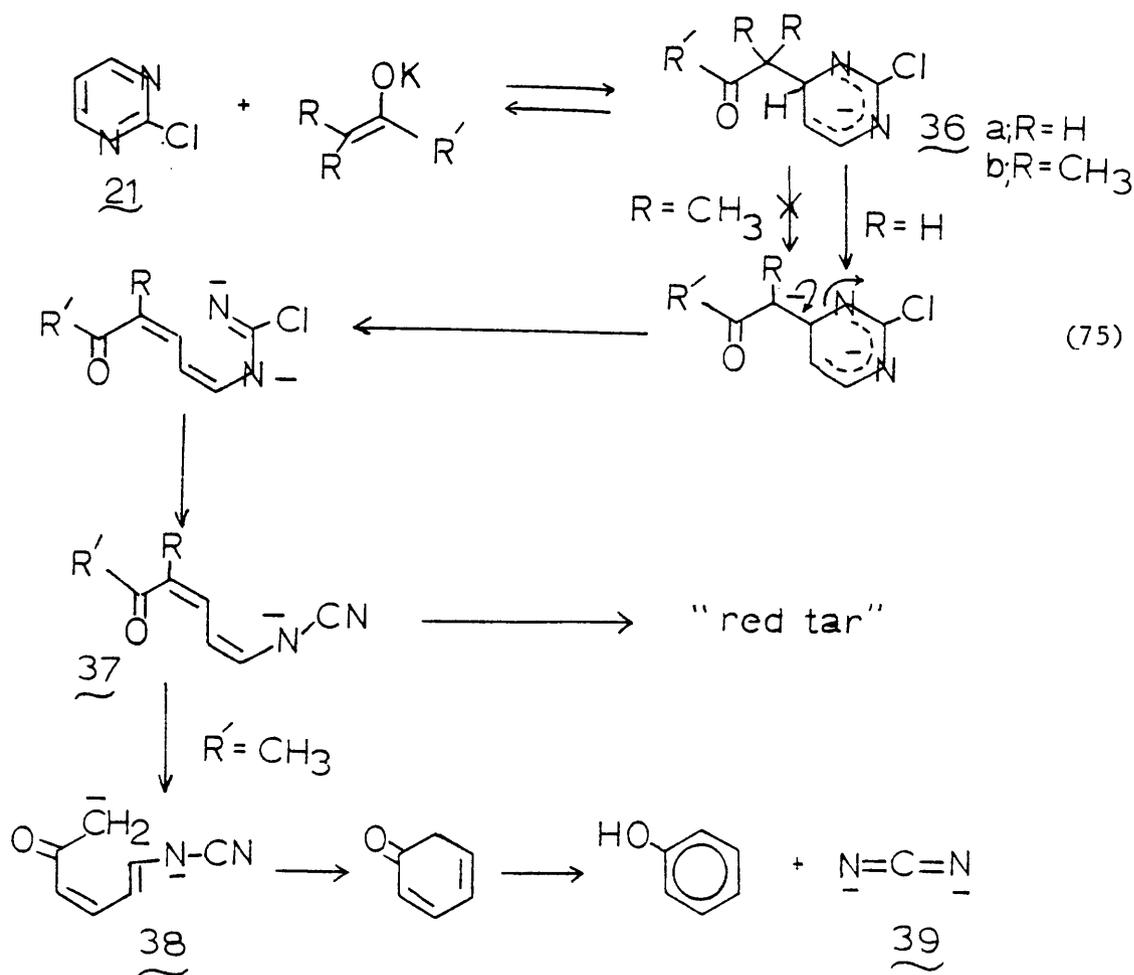
The dark reaction of 29 with pinacolone enolate resulted in no substitution product 30 but 80% of starting material was recovered. The reaction was definitely radical chain in character as evidenced by the inhibition of the photostimulated reaction by a catalytic amount (20 mol %) of DTBN. In this reaction 6% of the substitution product 30 was produced and 65% of starting material 29 was recovered.

The question as to why the tertiary enolate substitutes so well for chloride in 2-chloropyrimidine and the primary carbanions do not may be explained by the known $S_NANRORC$ mechanism shown below in eq. 74.¹²⁰



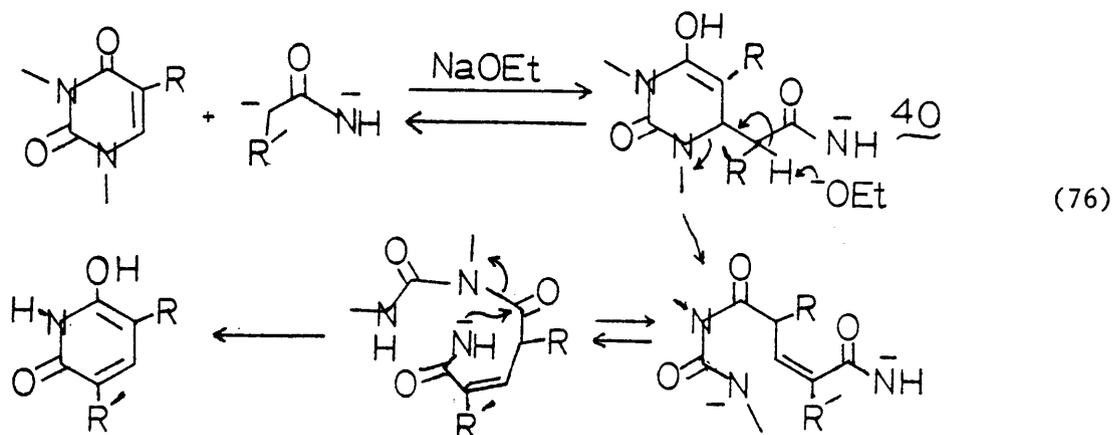
Initial addition of amide ion to the unhindered 4-position of the pyrimidine 31 to give 32 has been demonstrated. This monoanion has been postulated to ring open to give 33 or 34. Intermediate 34 may then close by intramolecular nucleophilic attack of the amino function on the nitrile to give, after subsequent proton transfers, the substituted aminopyrimidine.

In the case of the ketone enolates, initial attack at the 4-position of 2-chloropyrimidine to produce the σ -complex, 36, would occur (eq. 75). Further reaction of this intermediate would require



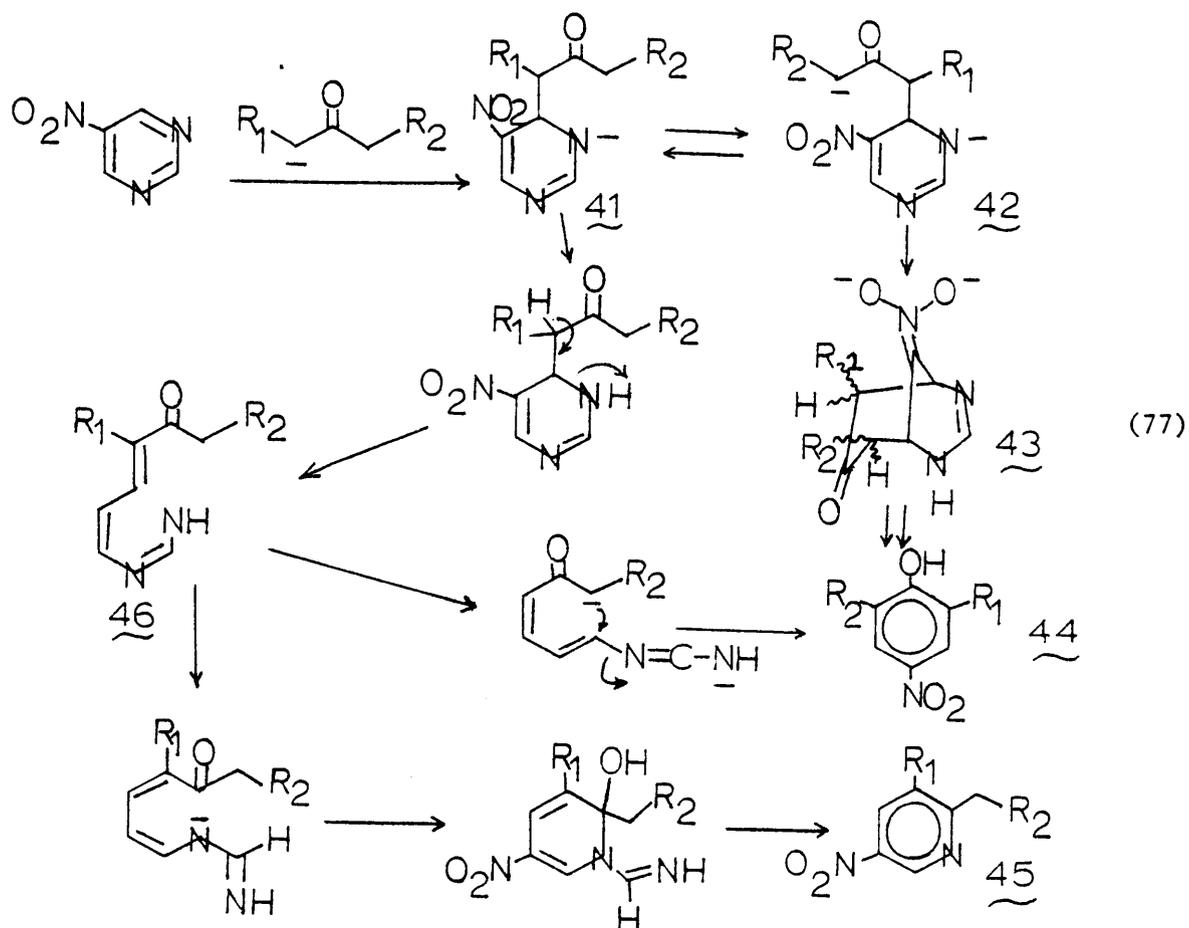
deprotonation of the carbon α to the carbonyl and the heteroaromatic ring. In the case of adducts formed from primary enolates (36a), this condition is fulfilled, and ring opened structures such as 37 could be intermediates. Unlike the case of 34 in which the amino substituent intramolecularly ring closed to ultimately give 2-amino-6-phenyl-pyrimidine, 37 evidently does not close to give any easily isolated product. Understandably this should be the case, since 37 is a delocalized anion, and the carbon that would ring close does not share a large portion of the charge. In the presence of excess base, this material may dimerize or form higher molecular weight materials. Alternatively, if R' is an ionizable group, as would be the case of acetone enolate, carbanion formation to give 38 and attack of the carbanion on the carbon containing the N-C-N linkage would eliminate the dianion of cyanamide (39). This evidently does not happen in this case, probably because intermolecular attack of enolate is faster than intramolecular cyclization or elimination of the dianion of cyanamide is unfavorable. Cyclizations of this type have literature precedence.¹²¹⁻¹²³

For example, the conversion of 1,3-dimethyl uracil derivatives into 2,6-dihydropyridines¹²³ proceeds through the S_N ANRORC mechanism (eq. 76). In this case the requirement for the nucleophile to be able to form the carbanion 40 was necessary for the process to take place. Also, the stabilization of the leaving fragment N-C-N was much greater than in the postulated route of



2-chloropyrimidine. The quaternary nitrogen in many of these ring transformations is crucial for the reaction process.^{121,124}

Additional literature data¹²² on the addition of ketones to pyrimidines is detailed below (eq. 77). In this scheme addition



compound 41 can open to give acyclic compound 46. An alternative discussed is the bicyclic bridged intermediate 43; however, no evidence was put forward to support such a claim. Ring closure can take place at two different sites to give 44 or 45. Elimination of the dianion of cyanamide is postulated for the formation of the phenol 44. In all cases the requirement for an acidic proton α to the ring prior to ring opening is found. In most mechanisms detailed by van der Plas, in 37 the protonation of the ring nitrogen in the initially formed σ -complex is not drawn into the mechanism. Evidence supporting protonation before or after the ring cleavage has not been put forward at this time.

It should be noted that the small amounts of aminopyrimidine formed in reactions of 2-chloropyrimidine with ketone enolates (eq. 69, 70, 71) was not a photolytic process. Published work indicates the substitution of halide in 2-bromo and 2-iodopyrimidine can take place by a photolytic non-chain radical process listed below.¹²⁵

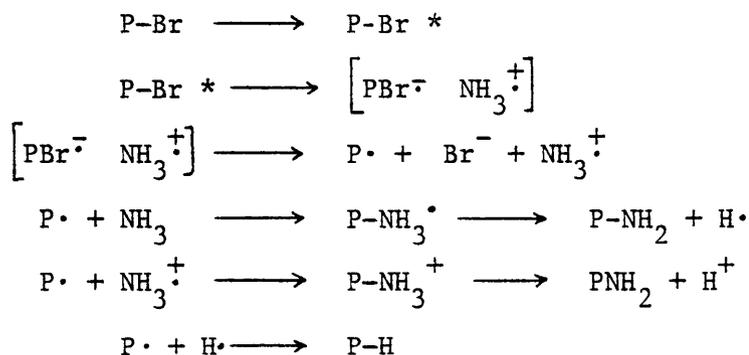


Table VII

Reaction of 3-Chloro-6-methoxypyridazine With
Ketone Enolates

| Expt. No. | Ketone | Conditions ^{a,b} | Product No. | Yield |
|-----------|--------------------------------------|------------------------------|-------------|--------|
| 13 | pinacolone | h ν | <u>47</u> | 5% |
| | | | <u>50</u> | 72% |
| 14 | pinacolone | dark | <u>47</u> | 24% |
| | | | <u>50</u> | 38% |
| 15 | pinacolone | dark, inhibited ^c | <u>47</u> | 70% |
| | | | <u>50</u> | 0% |
| 16 | diisopropyl ketone | h ν | <u>47</u> | 50% |
| | | | <u>48</u> | 13.3% |
| 16 | diisopropyl ketone | h ν ^d | <u>47</u> | 15% |
| | | | <u>48</u> | 17-20% |
| 17 | diisopropyl ketone | dark | <u>47</u> | 90% |
| 17 | diisopropyl ketone | dark ^{d,e} | <u>47</u> | 50% |
| 18 | acetone | dark | <u>51</u> | 60% |
| 19 | diisopropyl ketone and acetone | dark ^{f,b} | <u>51</u> | 19.3% |
| | | | <u>48</u> | 21.2% |
| 19 | diisopropyl ketone and acetone | dark ^{g,b} | <u>51</u> | 5% |
| | | | <u>48</u> | 31.5% |

^aReaction time 15 min.

^bRatio of enolate to substrate, 3.75:1

^c10 mol % of DTBN used as inhibitor

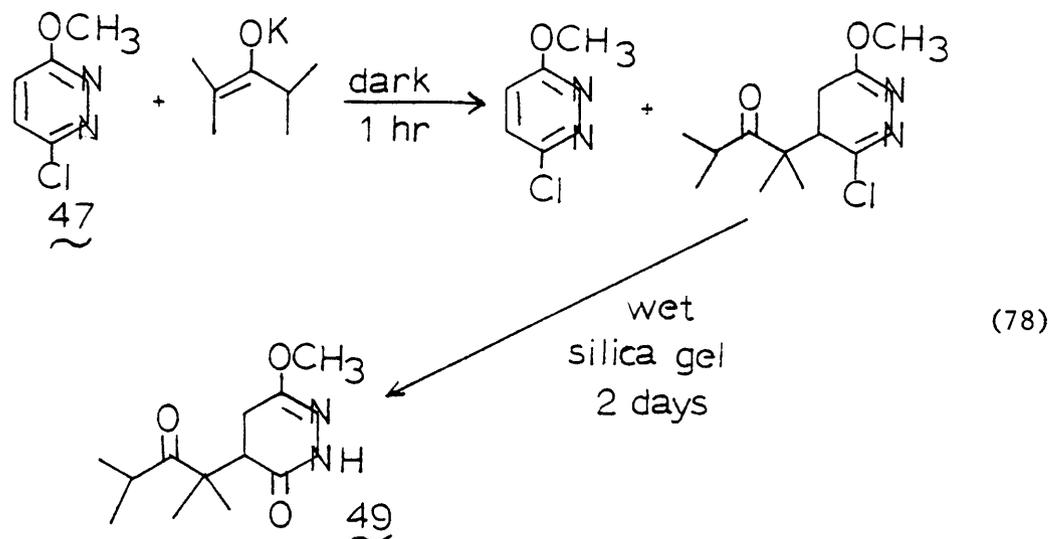
^dReaction time 1 hr.

^eReaction mixture treated with wet silica gel for 2 days

^fRatio diisopropyl ketone to acetone, 50:50

^gRatio diisopropyl ketone to acetone, 90:10

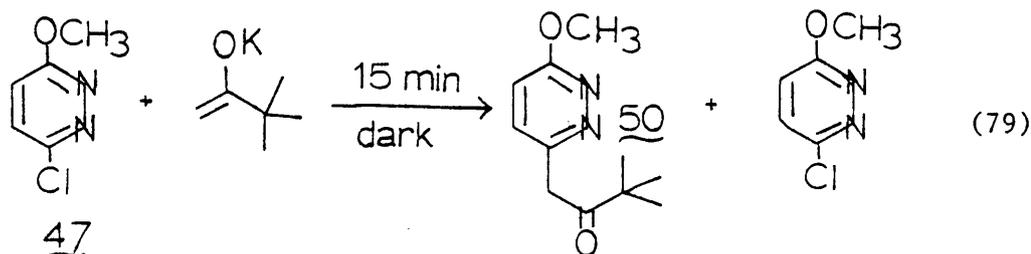
of 3-methoxyimidazole by a reductive process was not detected. The alternatives to substitution at the 3-position are: 1) photodecomposition; 2) a competing S_NAR2 reaction; 3) disubstitution (substitution at the methoxy as well as at the 3-position). A chromatographic search of the reaction material uncovered no trace of the disubstitution product, but the instability of the crude mixture to traces of acid or heat ($> 40^\circ\text{C}$) was noted. Such conditions of acid or heat produced a dark red tar that was chromatographically (TLC) immovable except with polar solvents such as methanol. Carefully controlled experiments yielded material which, after stirring with wet silica gel for two days, appeared to be the structure, 49, below (eq. 78).



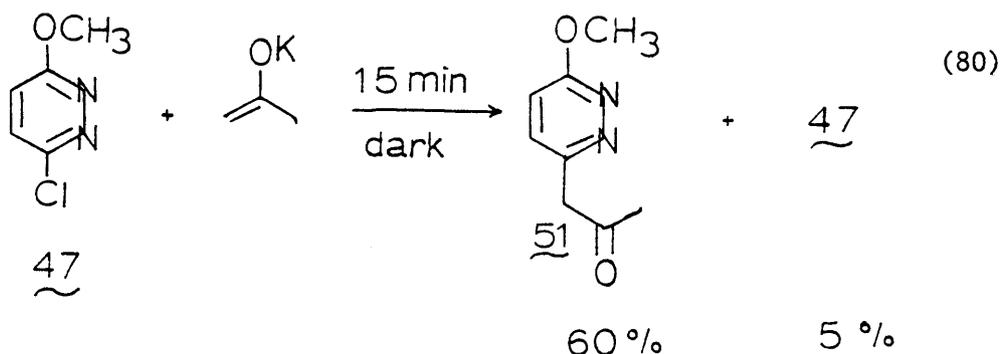
This material (49) was isolated from the dark reaction of the 3-chloropyridazine in low yield (8.3%). The consumption of starting material in the photostimulated reaction is much faster, and this

may be due to the σ -complex photolytically decomposing or substituting on the 3-chloropyridazine. Alternatively or additionally, the ipso substitution product may be photolytically unstable.

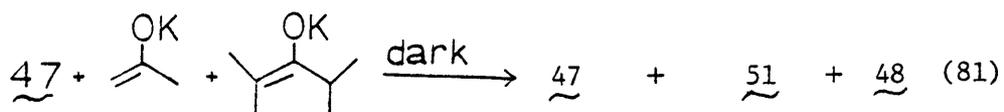
In contrast to the low reactivity displayed by diisopropylketone enolate, pinacolone enolate was more reactive toward 3-chloro-6-methoxypyridazine since it gave a 38% yield of substitution product (50) in a 15 min reaction in the dark (eq. 79). This yield could be



increased to 72% by photostimulation and completely inhibited by addition of a catalytic amount of di-*t*-butylnitroxide (Expt. no. 13 and 15, respectively; Table VII). Other primary enolates were tried. Acetone enolate displayed even greater $S_{RN}1$ reactivity by undergoing a 60% overall substitution in the dark in 15 min (eq. 80).



On first analysis we would expect the reactivity of diisopropyl ketone enolate to be greater than those of the primary enolates. The increased nucleophilicity of a tertiary enolate (and thus greater electron donating ability) and increased stability of the tertiary radical formed in the initiation step would seem to make this enolate more likely to react in the dark. If the chain lengths with acetone and pinacolone enolate were very long, then even a slight increase in a termination reaction such as hydrogen atom abstraction by the pyridazinyl radical intermediate could greatly reduce the chain length. If this happened in the case of diisopropyl ketone enolate, this would greatly slow the rate of substitution. To show what the problem was most likely with initiation and not propagation steps a series of entrainments were performed with acetone enolate and the tertiary enolate (eq. 81).



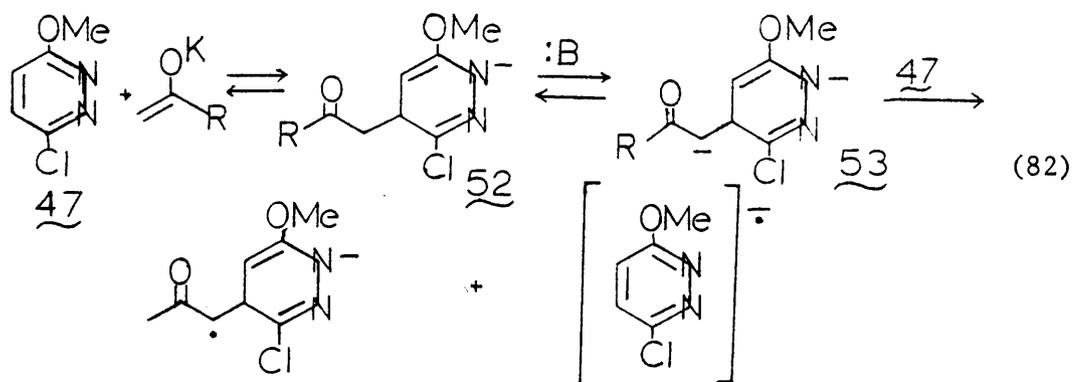
| | | | | |
|--------|-----------------|-----|-------|-------|
| molar | 1 : 1.75 : 1.75 | 5% | 19.3% | 21.2% |
| ratio: | 1 : .375 : 3.75 | 19% | 2% | 31.5% |

Stimulation of the reaction by the acetone enolate leads to the tertiary enolate propagating the chain reasonably well, as evidenced by the 31.5% yield of substitution of the ketone. This yield could probably be improved by inverse addition of the acetone enolate to a

stirred solution of the pyridazine and the diisopropyl ketone enolate. Of significance is the fact that in equimolar concentrations, the pyridazine radical showed no preference for the tertiary enolate. This result can be contrasted to those of Bunnett's¹²⁶ and Wolfe's.^{31,59c}

The 2-quinolyl radical^{59c} was found to be less reactive (more selective) than phenyl radicals in combining with nucleophiles; whereas the phenyl radicals displayed little selectivity towards carbon centers with presumed increased carbon density. 3-Pyridazinyl radical evidently falls in the category of phenyl radicals in terms of stability, if the selectivity-reactivity principal can be applied in these cases.¹¹⁵

The question as to the unusual reactivity of acetone may be explained in terms of formation of the σ -complex at the 4-position of pyridazine (eq. 82). In the case of acetone and pinacolone the



presence of an acidic proton in the σ -adduct **52** could possibly give a dianion such as **53**. This dianion would be a better electron donor than the enolate of pinacolone to the starting substrate and would stimulate the $\text{S}_{\text{RN}}1$ mechanism. In the case of diisopropylketone

enolate the two methyl groups prevent this ionization in 53, and therefore, the reaction does not get stimulated in these cases. The poor yield in the photostimulated cases points to another problem in initiation that may go beyond the presumption of the σ -adduct 52 being the stimulatory anion.

Another reason for the lowered reactivity of the tertiary enolate could be due to the steric and the dipole-dipole repulsion factor associated with the electron pairs on the pyridazine molecule. From the simplistic drawing (diagram 2) it can be seen that the

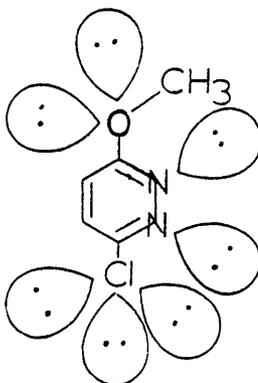


Diagram 2

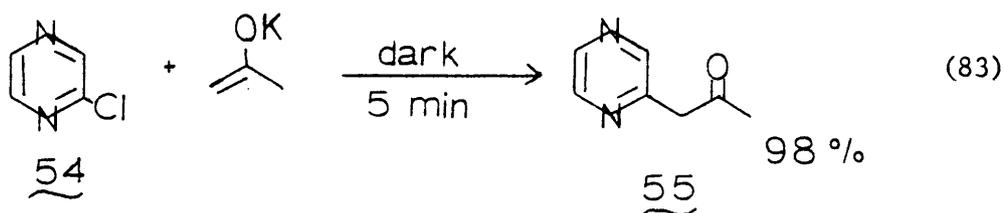
pyridazine molecule has a wealth of electron pairs confined to a localized volume of space. This fact coupled with the hindered nature of the enolate may prevent the initiation of the $S_{RN}1$ chain reaction. In the case of the acetone and pinacolone enolates the steric factor is reduced, and initiation of the $S_{RN}1$ reaction takes place.

Presumably the $S_{RN}1$ reaction is competitive with the ionic addition of the enolate to the 4- or 5-position of the pyridazine.

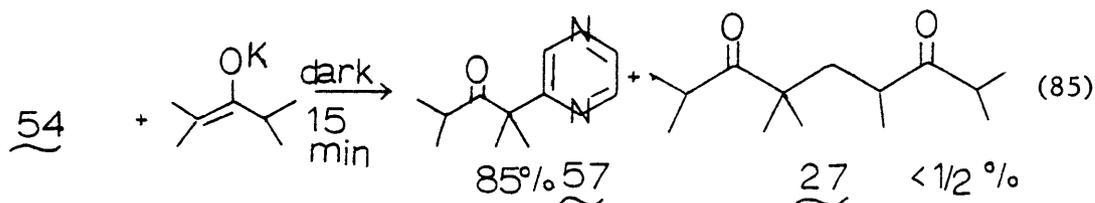
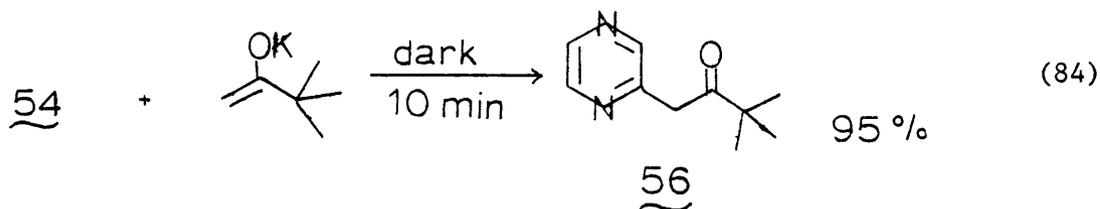
In the case of pinacolone, evaporation of the solvent of the inhibited reaction lead only to red tars. This may be due to dimerization of the σ -complex upon warming to room temperature or by S_N ANRORC processes that took place in the reaction.

C. Pyrazine

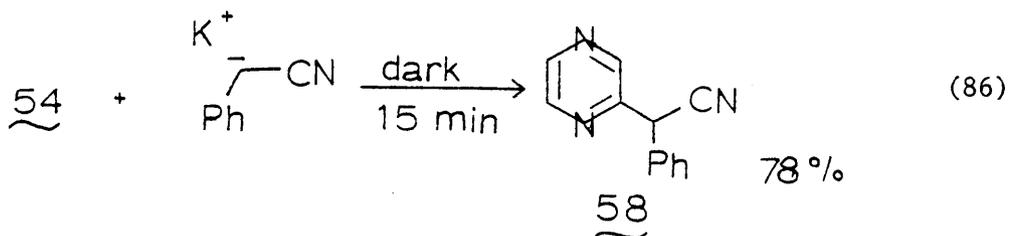
Several different carbanions were used to investigate the $S_{RN}1$ activity of 2-chloropyrazine. The results of these reactions are summarized in Table VIII. Reaction of 2-chloropyrazine (54) with acetone enolate in the dark in liquid ammonia proceeds in excellent yield (98%) to give the substituted product (55) via a radical-chain process (eq. 83). Introduction of a catalytic amount of the radical



scavenger (DTBN) completely inhibited formation of 55 (Ref. 128, Table VIII). Pinacolone and diisopropyl ketone enolates react in a similar manner (eq. 84 and 85) to give good yields of the substitution products. The diisopropyl ketone enolate produced only a very small amount ($< 1/2\%$) of the unsymmetrical ketone dimer, 27, and an undetectable amount of the reduced substrate, pyrazine.



Reaction of 2-chloropyrazine with potassiophenylacetonitrile under similar conditions to those used with acetone enolate (dark, 15 min, liquid ammonia) produced a good isolated yield (78%) of substituted product 58 (eq. 86). Addition of a catalytic amount



(20 mol%) of the inhibitor, DTBN, produced a decrease in the amount of substitution product 58 (38%). Reducing the reaction time to 3 min resulted in a 44% isolated yield of the product 58 in a dark reaction (expt. 22, Table VIII). Inhibition of the 3 min reaction

Table VIII

Reaction of 2-Chloropyrazine With Carbanions

| Expt. No. | Carbon Acid | Conditions ^{a,b} | Product | |
|-----------|-----------------------|--------------------------------|-----------|-------|
| | | | No. | Yield |
| Ref. 128 | acetone | dark | <u>55</u> | 98% |
| Ref. 128 | acetone | dark; inhibited ^c | <u>54</u> | 91% |
| | | | <u>55</u> | 0% |
| Ref. 128 | pinacolone | dark | <u>56</u> | 95% |
| 21 | diisopropyl ketone | dark | <u>57</u> | 85% |
| 22 | phenylacetonitrile | dark | <u>58</u> | 78% |
| 22 | phenylacetonitrile | dark ^d | <u>58</u> | 44% |
| 23 | phenylacetonitrile | dark; inhibited ^e | <u>58</u> | 38% |
| 23 | phenylacetonitrile | dark; inhibited ^{e,d} | <u>58</u> | 11% |
| 23 | phenylacetonitrile | dark; inhibited ^f | <u>58</u> | 77% |
| 24 | acetophenone | dark | <u>59</u> | 82% |
| 25 | acetophenone | dark; inhibited ^g | <u>59</u> | 0 |
| | | | <u>54</u> | 90% |

^aReaction time 15 min.

^bRatio of enolate to substrate, 3.75:1

^c10 Mol % of DTBN used as inhibitor

^dReaction time 3 min.

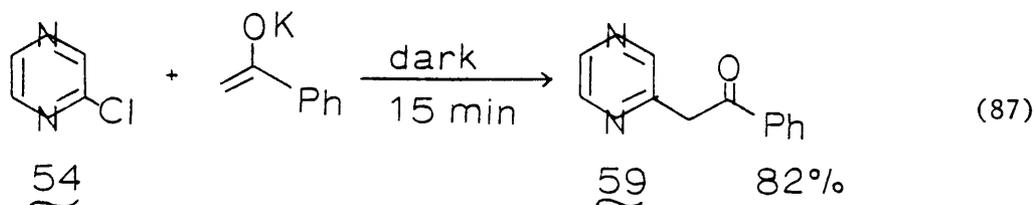
^e20 Mol % of DTBN used as inhibitor

^f10 Mol % of DNB used as inhibitor

^g15 Mol % of DTBN used as inhibitor

with 20 mol % of DTBN gave a 11% isolated yield of 58. Interestingly, addition of p-dinitrobenzene (DNB) to the reaction (to inhibit radical processes) produced no decrease in the yield of substitution product 58.

Decreasing the nucleophilicity of the anion still resulted in a good substitution on the 2-chloropyrazine. A 15 min reaction of the potassium salt of acetophenone in the dark with 2-chloropyrazine gave a 82% yield of substitution product 59 (eq. 87). Inhibition of this



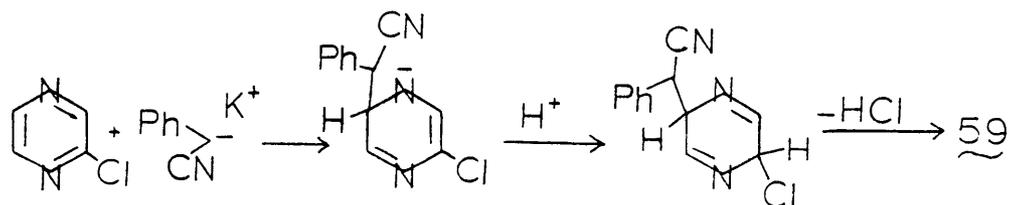
reaction with 15 mol % of DTBN completely retarded the formation of product 59, and a greater than 90% recovery of 2-chloropyrazine was noted.

From the reactions of the carbanions described above with 2-chloropyrazine, it is clear that 2-chloropyrazine does not require photostimulation for $S_{RN}1$ reactions. This can be contrasted to other aromatics such as pyridine and benzene derivatives that require photostimulation for $S_{RN}1$ mechanisms to operate. This is likely due to the increased electron affinity of pyrazine for reduction to the radical anion over that of pyridine or benzene.

The powerful nucleophile, potassiophenylacetonitrile, would be expected to undergo as facile $S_{RN}1$ substitutions on 2-chloropyrazine as acetone enolate. However, it was found that the phenylacetonitrile

anion required at least 15 min for the reaction to reach completion vs only 5 min for acetone enolate. Additionally, the phenylacetonitrile reaction was not completely inhibited by 20 mol % of DTBN. This could conceivably be due to only a $S_{RN}1$ reaction taking place. The number of initiations could be very large per unit time, and this could produce enough radicals (or radical anions) to completely consume the amount of scavenger present in the solution. After all scavenger was consumed, the reaction could proceed on to substituted product, but it would have a decreased yield due to consumption of 2-chloropyrazine radicals by the radical scavenger.

A more reasonable explanation would be a $S_{RN}1$ mechanism with a shorter chain length but more initiations in combination with a separate S_NAR2 pathway. Inefficient trapping of the radical intermediates by the di-*t*-butylnitroxide seems unlikely in light of the previous reactions with enolates. An alternative to the direct S_NAR2 pathway (AE_N) is the AE_a pathway depicted above. Evidence supporting or differentiating the two routes has not been investigated.



The reaction does not proceed at too great a rate to inhibit, since the 3 min reaction did not go to completion. The inhibition in this case supports a reaction with two independent reaction pathways, the $S_{RN}1$ and an AE type process.

Interestingly, addition of m-dinitrobenzene (DNB) to the reaction results in no decrease in the yield of substitution product. This is understandable since DNB is thought to act as an electron sink towards radical anions and thereby disrupt the chain process by destroying radical anions that would propagate the cycle. However, the electron reduction potential of chloropyrazine is probably less than that of DNB; thus, the radical anions would have no preference for DNB reduction. In the case of less easily reduced substrates such as pyridines, benzenes, and quinolines it would function effectively as an electron "sink."

The relatively weak nucleophile, acetophenone enolate, surprisingly substituted very well with 2-chloropyrazine. In previous cases (iodobenzene), acetophenone enolate failed to substitute for the nucleofuge. This was due (as experiments indicated) to the inability of the radical anion of the substitution product to propagate the chain. Understandably this is true, since the acetophenonyl group stabilizes the radical anion of the substitution product (of iodobenzene) to a greater extent than a typical alkyl ketone group. This stabilization is great enough so that the radical anion of the substitution product cannot reduce the aromatic halide to propagate the chain. With 2-chloropyrazine there was a different situation.

The radical anion of the substitution product in 2-chloropyrazine cases can propagate the chain because of the lower reduction potential of chloropyrazine.

The radical anion of phenylacetophenone (Diagram III, i) is considered to have the "extra" electron localized on the carbonyl.^{119a} The stabilization of this ketyl by the phenyl group is enough so that the transfer of an electron to the substrate (iodobenzene) is unfavorable.



This is reflected in the literature value of the reduction potential of acetophenone vs that of benzene.^{119b} With pyrazine the reduced reduction potential of chloropyrazine over that of iodobenzene enables the radical anion of substituted pyrazine (Diagram III, ii) to transfer the electron to the substrate (2-chloropyrazine). Conceivably, the radical anion of the substituted pyrazine may have the major portion of the spin density in the heteroaromatic portion of the molecule as drawn in Diagram III, ii.

D. Quinoxaline

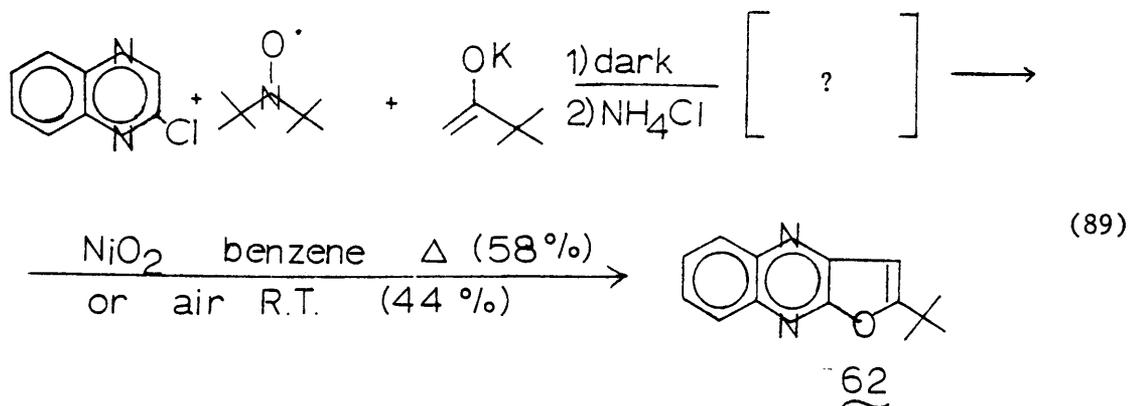
The $S_{RN}1$ activity of 2-chloroquinoxaline (60) was gauged with several ketone enolates, and the results of these reactions are summarized in Table IX. Reaction of 2-chloroquinoxaline with pina-

Table IX

Reaction of 2-Chloroquinoxaline with Ketone Enolates

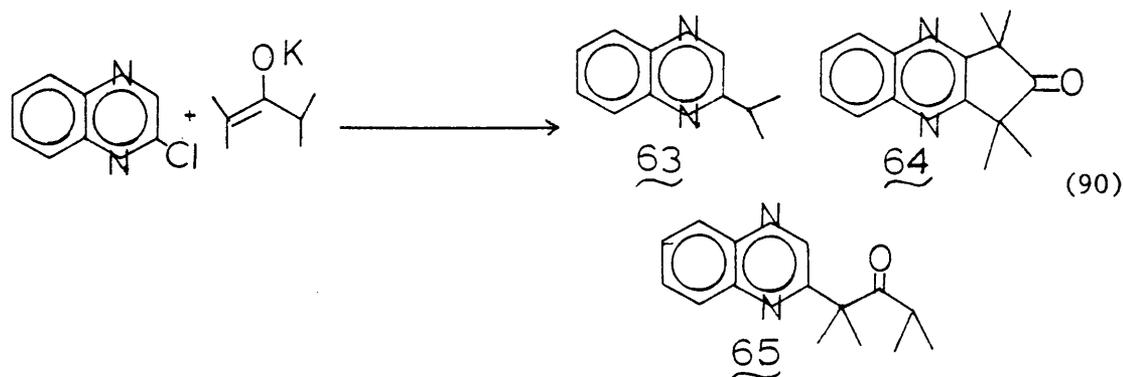
| Expt. No. | Ketone | Conditions ^{a,b} | Product | Yield |
|-----------|---------------------------|------------------------------|------------|--------------------------|
| 26 | pinacolone | dark | <u>62</u> | 15% |
| | | | <u>61</u> | 70% |
| | | dark ^c | <u>62</u> | 8.7% |
| | | | <u>61</u> | 70% |
| | | dark ^d | <u>62</u> | 11.3% |
| | | | <u>61</u> | 70% |
| 27 | | dark ^{e,c} | <u>62</u> | 18.1% |
| | | | <u>61</u> | 38.1% |
| | | dark ^{e,d} | <u>62</u> | 27% |
| | | | <u>61</u> | 26% |
| | | dark ^f | <u>62</u> | 43.5% (58%) ^g |
| | | | <u>61</u> | 0% |
| 28 | diisopropyl ketone | dark | <u>63</u> | 17.3% |
| | | | <u>64</u> | 28.4% |
| | | | <u>65</u> | 31% |
| | | dark ^h | <u>65</u> | 43.4% |
| 29 | 3-methyl-2,4-pentanedione | dark | <u>60</u> | 47% |
| | | | <u>68a</u> | 15% |
| 30 | | hv | <u>60</u> | 45% |
| | | | <u>68a</u> | 17% |
| 31 | | dark; inhibited ⁱ | <u>60</u> | 51% |
| | | | <u>68a</u> | 3% |
| 32 | ethyl malonate | dark | <u>60</u> | 95% |

^aReaction time 15 min.^bRatio of enolate to substrate, 3.75:1.^cReaction time 3 min.^dReaction time 1 min.^e20 mol % of DTBNused as inhibitor. ^f100 mol % of DTBN used as inhibitor^gCrude reaction mixture treated with NiO₂ in refluxing benzene^hRatio of enolate to substrate 1:1. ⁱ15 mol % of DTBN used as inhibitor.



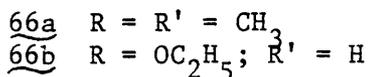
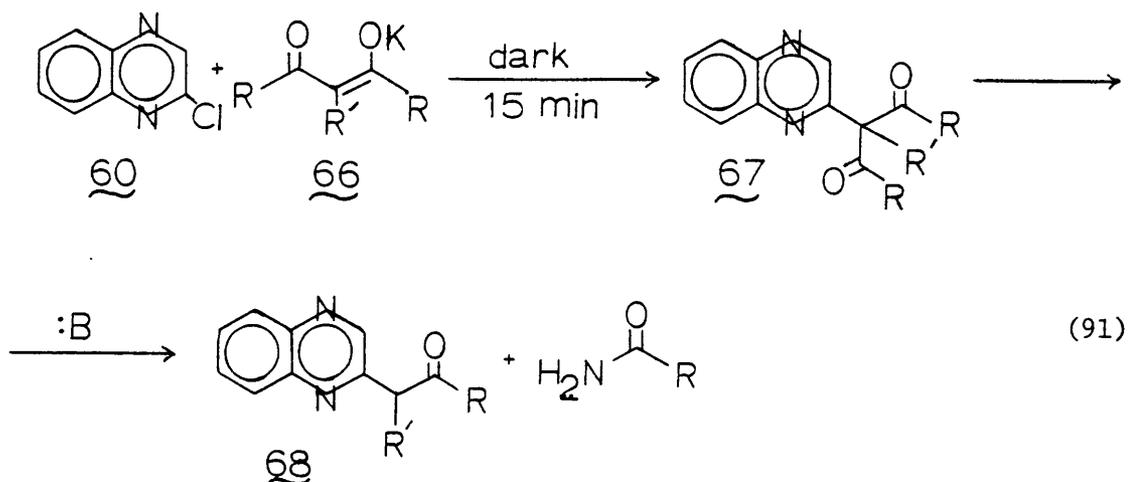
hypothesis, 61 was treated with one equivalent of KNH_2 in NH_3 for 15 min. No furoquinoxaline 62 was formed and 61 only was recovered (expt. 33).

Reaction of 2-chloroquinoxaline with 3.75 eq. of diisopropyl ketone enolate under dark conditions in ammonia gives several products besides the ipso substitution product 65. Besides a 31% yield of 65, 17.3% of 2-isopropylquinoxaline (63) and 28.4% of quinoxalin-[b]-ylcyclopentanone (64) were isolated (eq. 90).



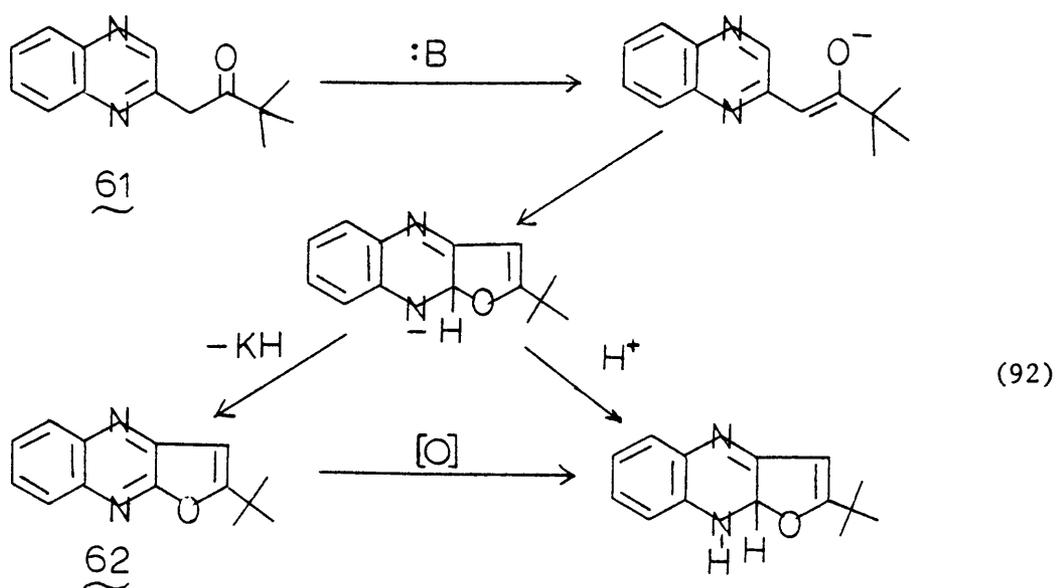
Using only one equivalent of diisopropyl ketone enolate resulted in a 43% yield of the substitution product 65, with no trace of the other products (63 and 64).

Reaction of 2-chloroquinoxaline with β -diketone monoenolates gave products of substitution in dark reactions. 3-Methyl-2,4-pentandione enolate (66a, $R=R'=\text{CH}_3$) with 2-chloroquinoxaline underwent reaction to give a substitution product (68). However, this was the only isolated product of substitution. Apparently cleavage of the intermediate 67 was very facile under the reaction conditions (eq. 91).

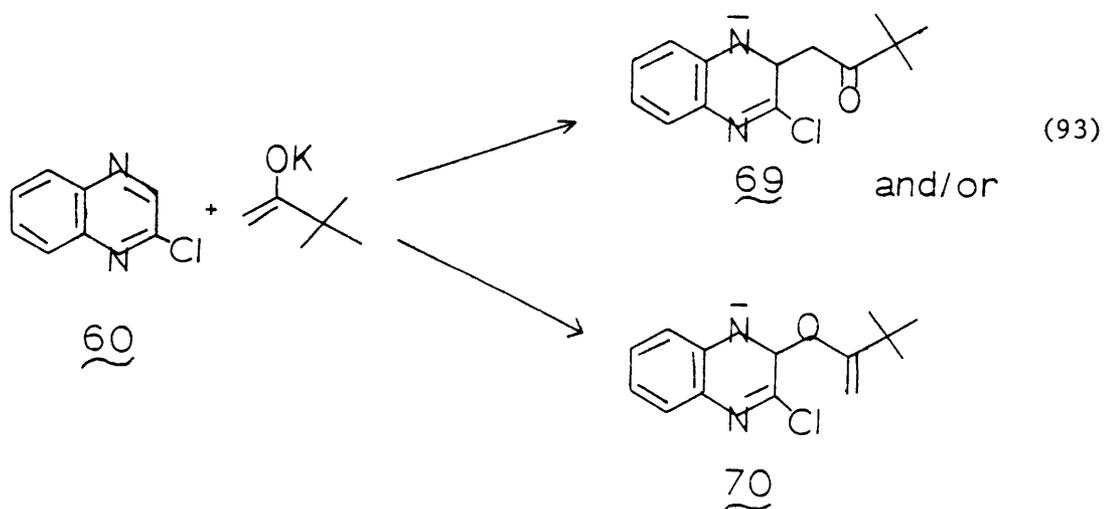


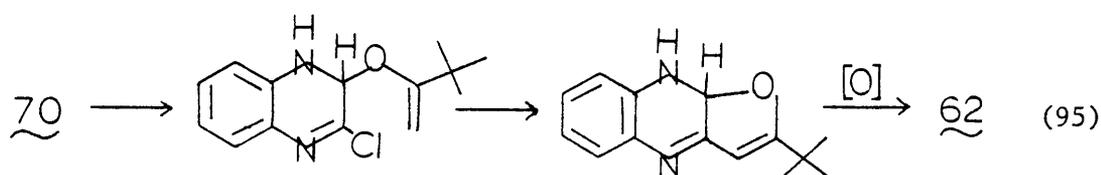
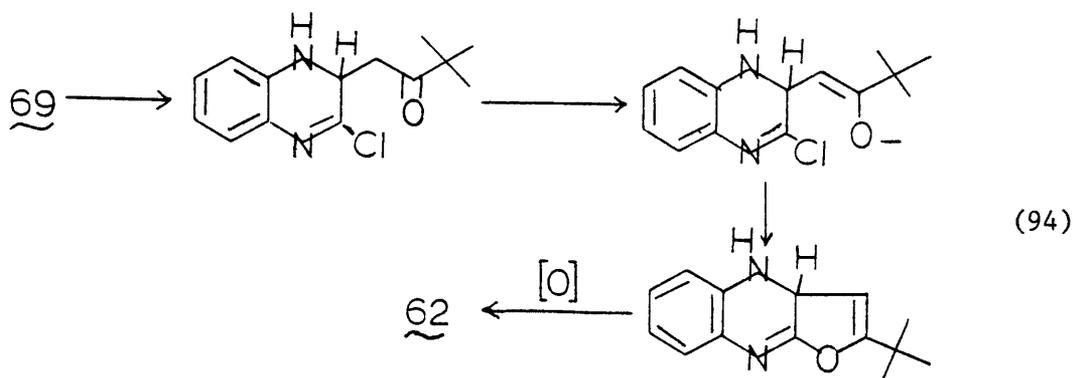
Again the process was shown to be radical in character by 15 mol % of DTBN inhibiting the formation of the cleaved substitution product 68 (expt. 31, Table IX). Surprisingly, ethyl malonate anion (66b, $R' = \text{H}$; $R = \text{OC}_2\text{H}_5$) gave no reaction with 2-chloroquinoxaline; although it is a stronger base than the 3-methylacetylacetonate anion (expt. 32, Table IX).

To explain the formation of the furoquinoxaline 62 in the reaction of pinacolone enolate with the chloroquinoxaline, the sequence of events shown below was thought to occur (eq. 92).



However, since the substitution product 61 was shown not to give the furoquinoxaline under the reaction conditions, this scheme was discounted. Also the fact that the furoquinoxaline showed no inhibition by DTBN, but the substitution product 61 did, indicated that the furoquinoxaline arose from an independent pathway such as the equations shown below demonstrate (eq. 93-95).

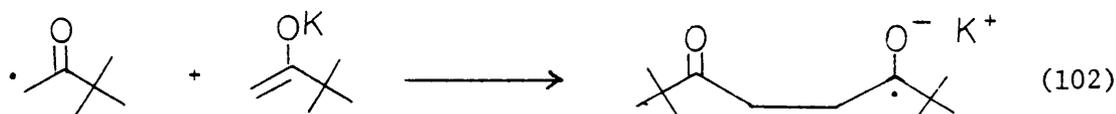
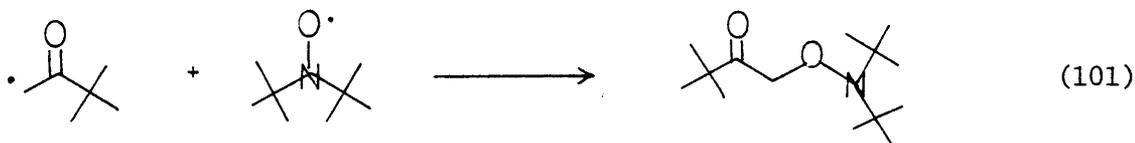
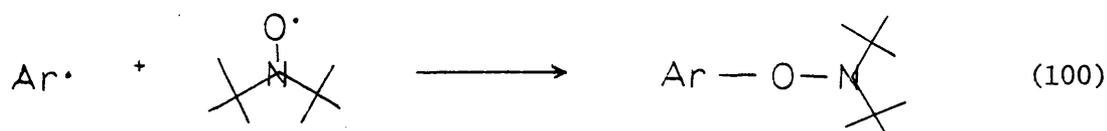
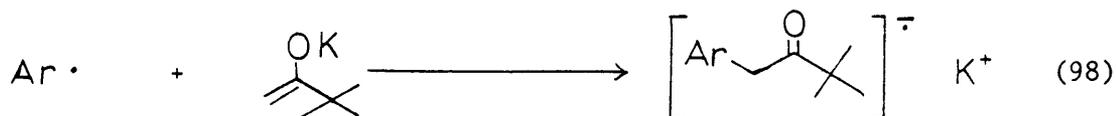
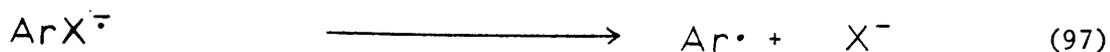
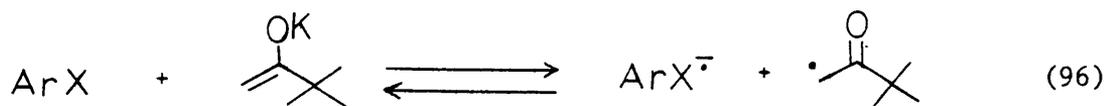


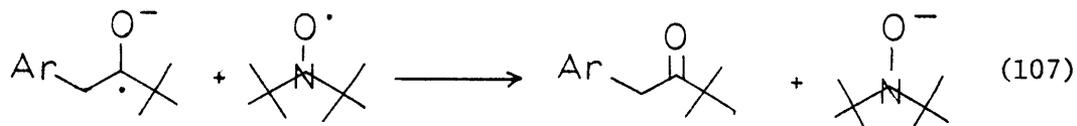
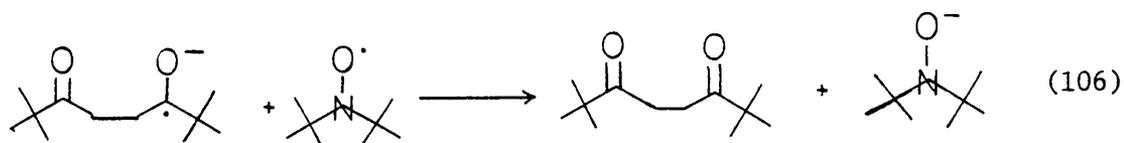
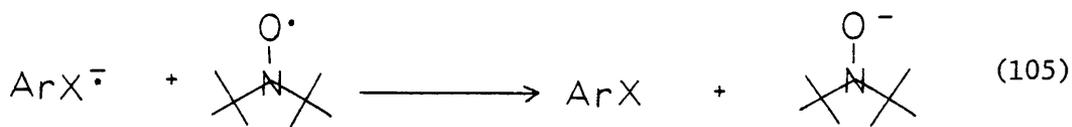
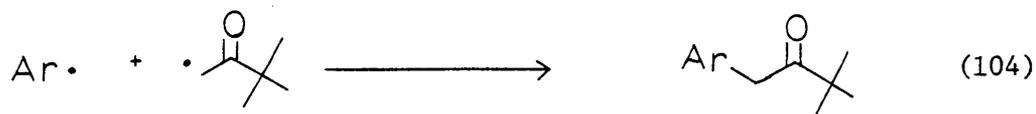
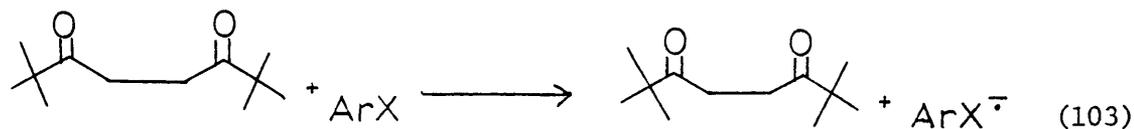


The key step in this sequence is the attack of the enolate at the 3-position of 2-chloroquinoxaline (eq. 93). This addition could conceivably be either C- (69) or O- (70) alkylation. Subsequent proton transfers give the dihydroquinoxalines 71 or 72 which are air oxidized (or preferably oxidized with NiO_2) to the fully aromatic system, 62.

The mechanism, by which the substitution product 61 of pinacolone and 2-chloroquinoxaline is formed, was definitely radical in character. This was shown by the complete inhibition of the product 61 by a full equivalent of radical scavenger (DTBN). Since the smaller percentages of inhibitor had the effect of incompletely inhibiting the formation of substituted product, this implies that there must be

a large number of initiations to produce enough radicals to consume the radical scavenger. Consider the following steps (eq. 96-107):





If the substitution product arises purely from the electron transfer process in which (eq. 96) the radical ion of chloroquinoline and pinacolone radical diffuse away from each other (break out of solvent sphere), then the question of the chain length centers around the stoichiometry of inhibitor required for quenching. If we assume that radical anion quenching by di-*t*-butylnitroxide is slow compared to radical trapping (eq. 105-107), then it is likely that two molecules of inhibitor are consumed per initiation. One molecule

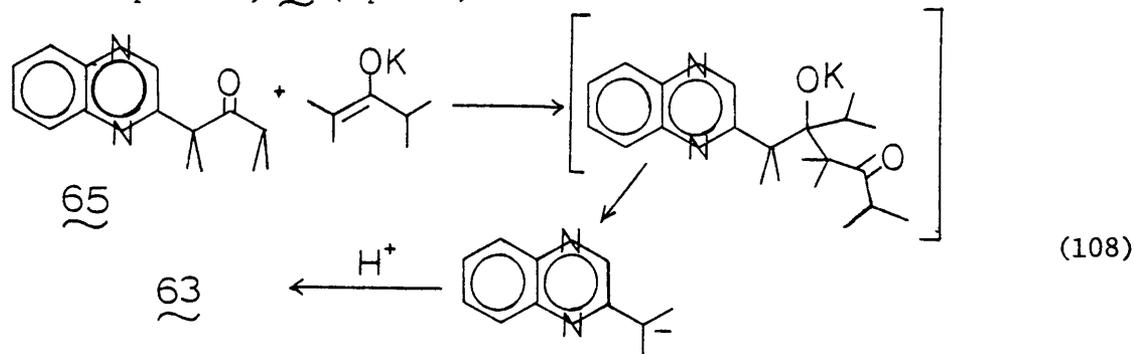
would be used to quench the quinoxaliny radical, and one would be used to quench the pinacolone radical (eq. 100 and 101, respectively). Combination of the pinacolone radical with an enolate, as diagrammed in eq. 102, to give the radical anion of the symmetrical dimer is unlikely in the presence of the inhibitor.

Taking these points into consideration, then in the 1 min , 20 mol % DTBN inhibited reaction there must have been at least 10% of the quinoxaline reduced by electron transfer to give pinacolonyl and quinoxaliny radicals. In the uninhibited case this produced a 70% yield of substitution product 61 versus a 26% yield in the inhibited case, giving roughly 40% inhibition in the same time period. Of course, once the inhibitor was consumed the other competing ionic processes had reduced the concentration of 2-chloroquinoxaline relative to what it would have been in an uninhibited case. Discounting that fact, the chain length in this radical reaction is qualitatively around four.

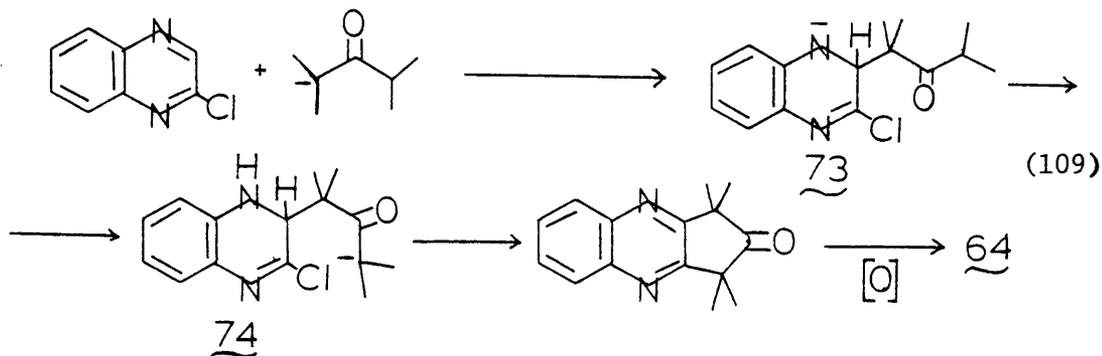
The indications of this reduced chain length, but still very fast reaction rate, is a reflection of the ease with which reduction of the 2-chloroquinoxaline can take place. The reaction proceeds in the dark and at a rate that is almost too fast to inhibit. Both factors point to the fact that initiation of the $S_{RN}1$ reaction in quinoxaline is very facile.

Reaction of diisopropyl ketone enolate with 2-chloroquinoxaline gave several products besides the ipso substitution product 65. The isopropylquinoxaline can be envisioned to be produced by the substitution product 65 by basic cleavage. Nucleophilic attack on the

carbonyl by the excess of enolate and then expulsion of the stabilized quinoxalinyll- α -anion would upon protonation give the observed product, 63 (eq. 108).



The formation of the quinoxalinyllcyclopentanone (64) may occur by a mechanism similar to that by which the furoquinoxaline was formed (eq. 109). The cleavage product 63 and the quinoxalinyll-



cyclopentanone were not formed when only one equivalent of diisopropyl ketone was used. This implies that cleavage of the substitution product 65 proceeds by attack of the enolate, not ammonia or amide to give isopropylquinoxaline. The lower yield of substitution product 65 (43%) and the lack of cyclization product 64 shows that excess base is necessary for further ionization of intermediate 73 to 74. Without this excess base intermediate such as 74 cannot form, and 73 was not detected in these experiments.

Because of the ease with which 2-chloroquinoxaline can be reduced to its radical anion, the β -diketone 66a was able to substitute on the heteroaromatic (eq. 91). Photostimulation of the reaction helped facilitate the reaction somewhat, but did not appear to be a major factor that helps, as it is in other systems. The β -diketone anion is not able to reduce aromatic substrates such as benzene and pyridine, but in the case of 2-chloroquinoxaline this did occur since the inhibited experiments indicated that the reaction proceeds by a radical mechanism (exp. 31, Table IX).

Ethyl malonate failed to substitute on the 2-chloroquinoxaline (exp. 32, Table IX). This was surprising since the diester monoanion should be a stronger base (and presumably a better electron donor) than a β -diketone monoanion.

E. Quinazolines

The reactions of 4-chloroquinazolines with pinacolone enolate are listed in Table X. Reaction of 4-chloro-2-phenylquinazoline (Am-ex-01,⁹¹ 75a) with pinacolone enolate in liquid ammonia in the dark gave an excellent yield of the substituted quinazoline 76a (eq. 110, 93%).

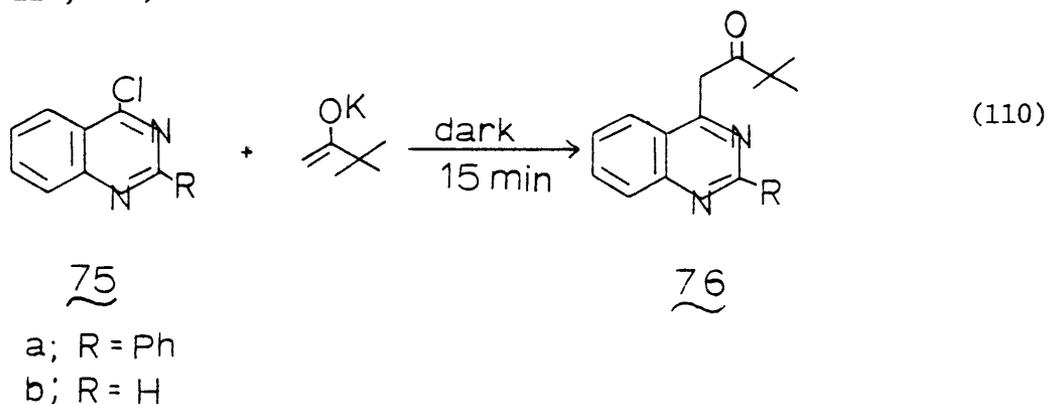


Table X

Reaction of 4-Chloroquinazolines With Pinacolone Enolate

| Expt. No. | | Conditions ^{a,b} | Product No. | Yield |
|--------------|-----------------------------------|---------------------------|----------------|-------|
| 34 | 4-chloro-2-phenyl- quinazoline | dark | <u>76a</u> | 93 |
| 35 | 4-chloro-2-phenyl- quinazoline | dark; inhibited | <u>76a</u> | 97 |
| 36 | 4-chloroquinazoline | dark | <u>76b</u> | 95 |
| 37 | 4-chloroquinazoline | dark; inhibited | <u>76b</u> | 95 |

^aReaction time 15 min.

^bRatio of enolate to substrate, 3.75:1

^c20 mol % of STBN used as inhibitor

There was absolutely no indication of any inhibition by di-*t*-butyl-nitroxide, since addition of 20 mol % of DTBN to 75a in reaction with pinacolone enolate produced a 97% isolated yield of substitution product 76a (expt. 35, Table X). Examination of 4-chloroquinazoline was performed to see if the phenyl substituent present in 75a had an anomalous effect on the substitution mechanism.

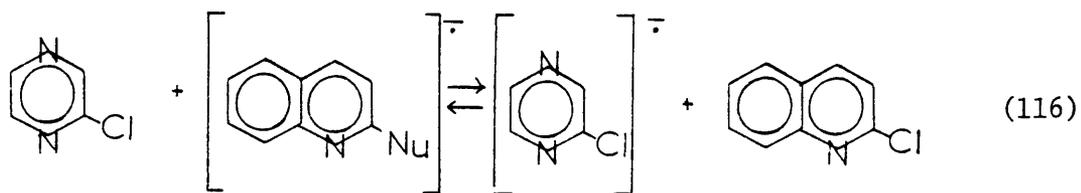
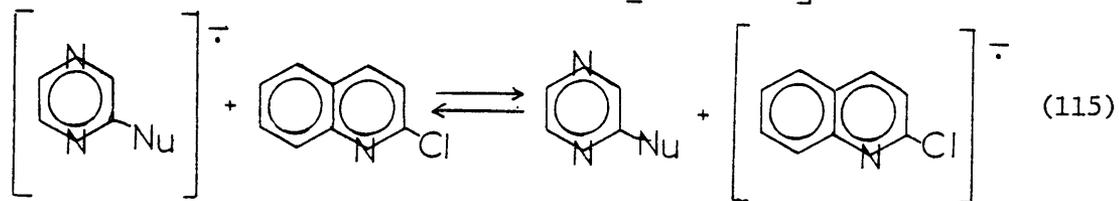
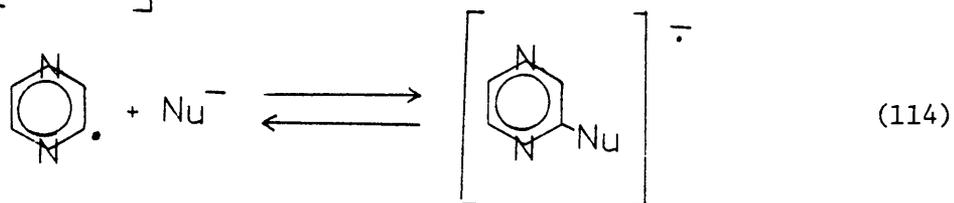
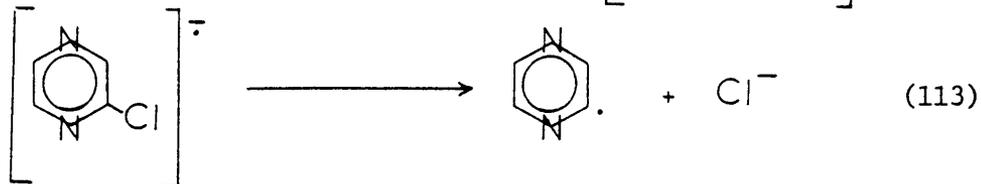
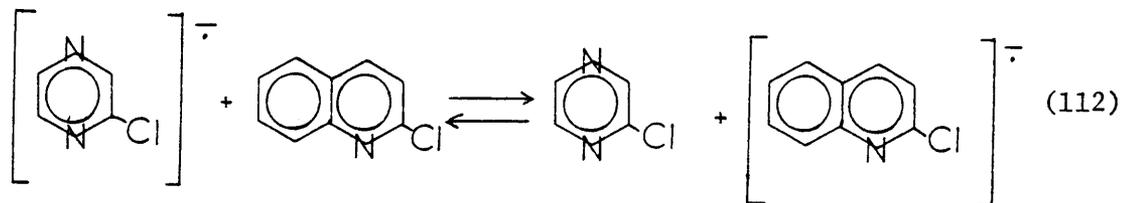
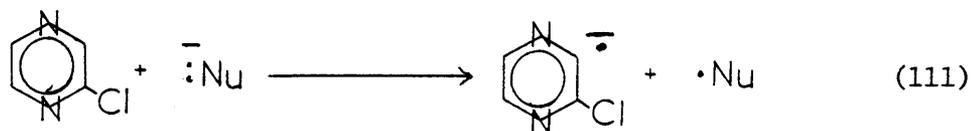
Reaction of 4-chloroquinazoline (75b) with pinacolone enolate (expt. 36, Table X) gave an excellent yield (95%) of substitution product 76b. Addition of 20 mol % of DTBN produced absolutely no change in the amount of substitution in this reaction (expt. 37, Table X), and a 95% yield of 76b was isolated in this case.

These experiments indicate that there is no radical or radical-chain process taking place in this substitution reaction (at least within experimentally defined error limits). So, from analogy with other substitutions, the mechanism can be assumed to be purely a $S_{\text{N}}\text{AR}2$ process.

F. Entrainments

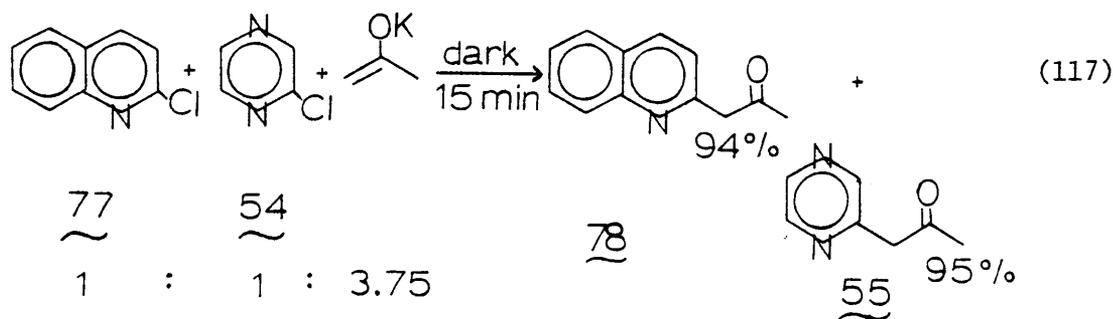
From the preceding sections it was found that some aromatics such as pyridine, pyrimidine, quinoline, and pyridazine underwent substitution reactions by the $S_{\text{RN}}1$ mechanism, but they required photostimulation for the reaction to proceed. Other heterocycles such as pyrazine and quinoxaline reacted smoothly via a radical route without photostimulation. Consideration of those points lead to the speculation that if some of these reactions proceed without irradiation, then other $S_{\text{RN}}1$ reactions could be stimulated without light by

substrate entrainment. That is, addition of a small amount of the substrate (haloaromatic) that reacts in the dark to the haloaromatic that requires light produces substitution on both aromatics. This is illustrated below with 2-chloropyrazine acting as an initiator for the radical process on 2-chloroquinoline (eq. 111-115).

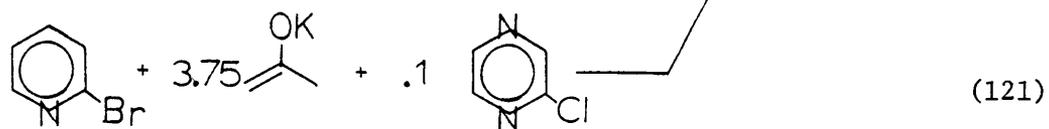
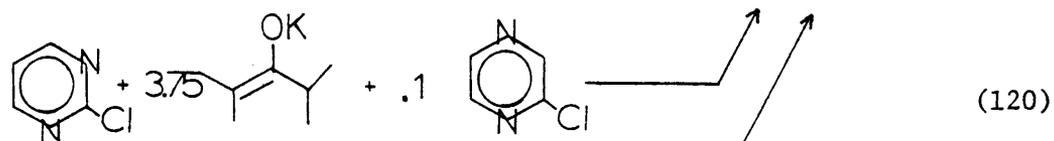
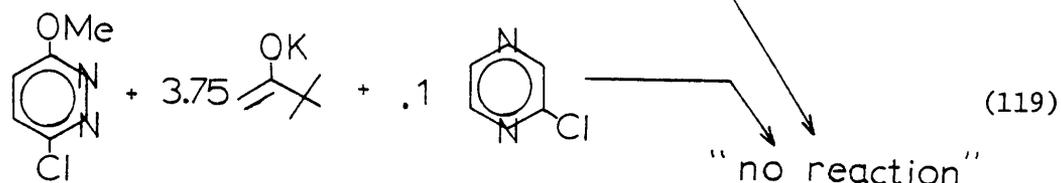
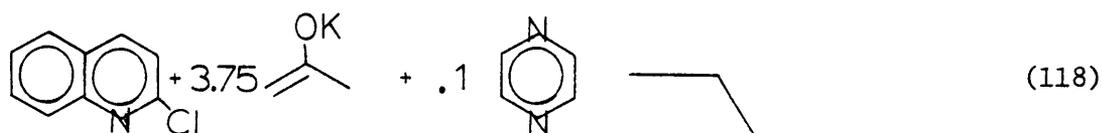


In eq. 111 the reduction of chloropyrazine can occur in the dark to give the radical anion. This radical anion might reduce the 2-chloroquinoline by electron transfer (eq. 112). The radical anion of 2-chloroquinoline thus formed would react in the usual sequence of propagation steps. Alternatively, the radical anion of the substituted pyrazine (eq. 115) could reduce the 2-chloroquinoline to initiate substitution on the quinoline molecule. Clearly, for the entrainment to succeed the radical anions of the pyrazinyl compounds must exhibit some degree of non-selectivity. They must show at least a small amount of electron transfer to the 2-chloroquinoline, or no substitution on 2-chloroquinoline will result. In addition, the quinolinyl radicals and radical anions must carry the chain back to the chloroquinoline (reverse of eq. 112 and 115 as well as eq. 116 must be slow). If these conditions are met in a reaction of this type, then it may be possible to stimulate a normally photostimulated reaction to a dark reaction; a condition that is easier to perform experimentally.

The following reaction was performed to test these conditions of electron transfer (eq. 117):

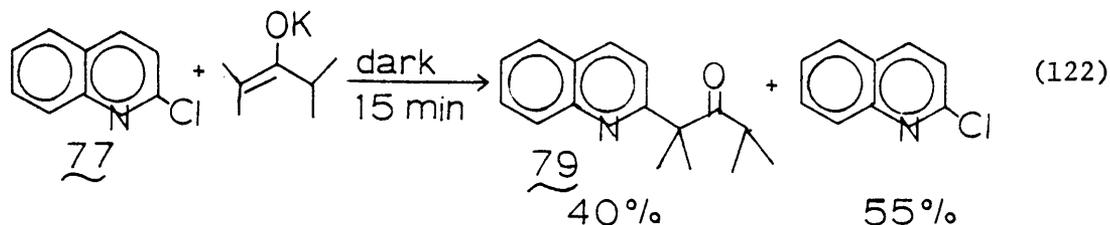


The reaction of 2-chloroquinoline with acetone enolate does not proceed to a significant extent in the dark. However, with 11 mol % of 2-chloropyrazine added the overall substitution process on 2-chloroquinoline proceeded quite well. With this success other entrainments and nucleophiles were tried as shown in eq. 118-121 (expt. 40-43).



In these cases "no reaction" implies that no increased amount of substitution was found over that of the dark unstimulated reaction. Interestingly, it was found that 2-chloroquinoline underwent a dark $S_{RN}1$ reaction with diisopropylketone enolate without any stimulation

(eq. 122). Thus, it appears that 2-chloroquinoline is a finely



tuned molecule on the verge of electron transfers that proceed with only thermal stimulation. So, increasing the electron donating power of the enolate sends it into a $S_{RN}1$ reaction or generation of pyrazinyl radical anions stimulate such processes.

In the other cases, the pyrazinyl radical anions evidently do not have sufficient reducing power to form the radical anions of the more difficult to reduce heterocycles. 2-Chloroquinoline was not stimulated by the parent heterocycle pyrazine for either or both of two reasons: 1) the reduction potential of pyrazine is higher than that of 2-chloropyrazine and the radical anion of pyrazine is not formed in the dark or 2) the electron transfer from pyrazine to quinoline does not take place. If the latter were the only reason the reaction did not proceed, then this would indicate that eq. 112 is not a major mode of electron transfer in these entrainments.

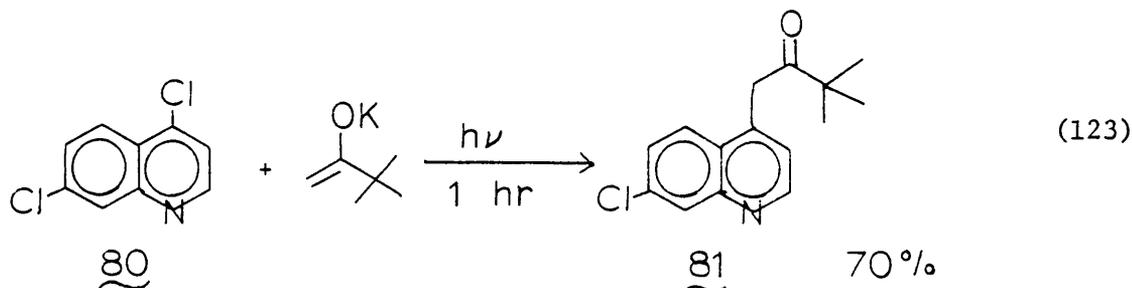
G. Dihaloaromatics

As mentioned in an earlier section, previous studies have shown that dihaloaromatics react with nucleophiles to form products in which both halogens are substituted by the nucleophile. This is due

to the radical anion of the monosubstitution product decomposing to form the radical and then nucleophile coupling to form disubstitution product without building-up of the monosubstitution product. These results implied that the reaction of dihaloaromatics in the diazine series would be a sensitive test for the presence of the radical anion intermediate and the $S_{RN}1$ reaction mechanism. Surprising observations were made in the reaction of 4,7-dichloroquinoline with pinacolone enolate.

1. Quinoline

Reaction of 4,7-dichloroquinoline (80) with pinacolone enolate resulted in the formation of monosubstitution product 81 in 70 % yield (eq. 123). However, the reaction was inhibited by catalytic



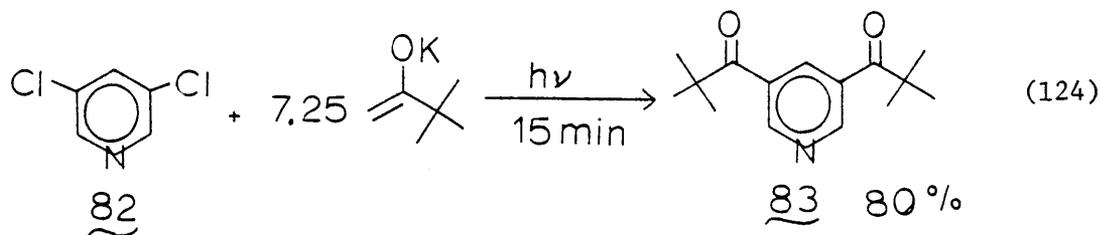
amounts of di-*t*-butylnitroxide. The interpretation in this case seems to point to the fact that the radical anion of the monosubstitution product 81 will transfer its high energy electron to another unreacted aromatic substrate (80) faster than the remaining nucleofugic group will diassociate from the aromatic nucleus of the radical anion. In this case why is the 7-position on the quinoline nucleus any different from previous (benzene) cases studied?

ESR experiments have shown that the free electron density in the parent quinoline molecule is very low at the 7-position, but not at the 4-position.¹²⁷ This decreased electron density at the 7-position in the radical anion of 81 may be responsible for the electron transfer to another aromatic molecule to compete with the fragmentation of the radical anion of 81 into the quinolinyl radical and halide anion. Once electron transfer occurs ionization of the carbon α to the carbonyl and the ring in 81 prevents any subsequent electron transfers due to the higher reduction potential of the resulting anion of 81.

2. Pyridine

In pyridine similar results to quinoline were expected. Studies show that the spin density in the radical anion of pyridine is highest at positions 2, 4, and 6 and lowest at 3 and 5.¹²⁸ As the results in the Table XI show, these expectations were not fulfilled. In 2,6-, 3,5-, 2,3-dichloropyridine, and 2,5-dibromopyridine disubstitution was found to be the predominate product. These results are summarized in Table XI.

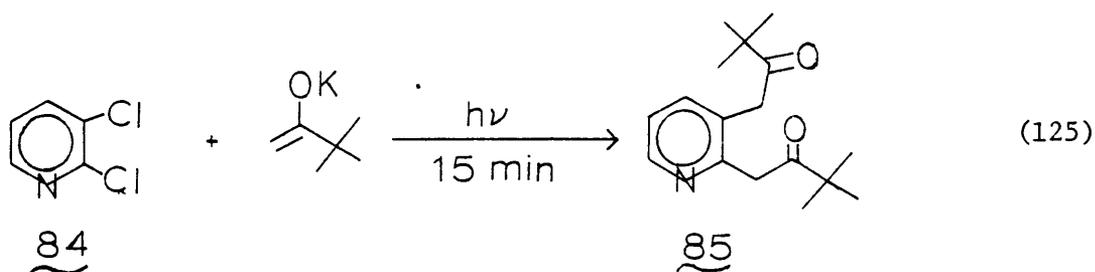
Photostimulated reaction of 3,5-dichloropyridine (82) with pinacolone enolate gave disubstitution product 83 (80%) after 15 min of irradiation (eq. 124).



The yield of 83, the only substitution product isolated, was reduced to 15.4% when 20 mol % of DTBN was added to the photo-stimulated reaction (expt. 54, Table XI). Also, 50% of the starting material 82 was recovered.

A 15 min dark reaction of 3,5-dichloropyridine produced 20% of 83 and 60-70% of 82 was recovered.

Pinacolone enolate under photostimulated conditions with 2,3-dichloropyridine (84) reacted to give 76.4% of disubstitution product 85 and almost complete consumption of the starting material (eq. 125). Dark reaction of this pyridine and the enolate produced



very little of substitution product 85 and a 70-80% recovery of 2,3-dichloropyridine (84).

When 2,5-dibromopyridine (86) was submitted to the photostimulated conditions with pinacolone enolate for 15 min, it too gave a good yield of disubstitution product 87 (85-90%) with complete consumption of the dihalopyridine (eq. 126). The dark reaction of

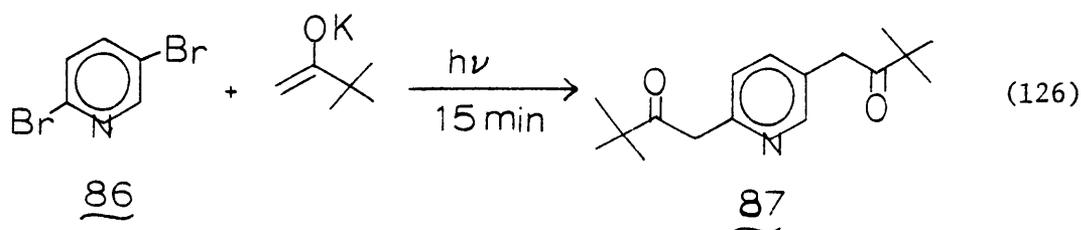


Table XI

Reactions of Dihalopyridines with Pinacolone Enolate

| Expt. No. | Pyridine | Conditions ^{a,b} | Product. No. | Yield |
|--------------|--------------|----------------------------|------------------------|---------------|
| 53 | 3,5-dichloro | hv | <u>83</u> | 80% |
| 54 | 3,5-dichloro | hv; inhibited ^c | <u>82</u> <u>83</u> | 50% 15.4% |
| 55 | 3,5-dichloro | dark | <u>82</u> <u>83</u> | 60-70% 20% |
| 56 | 2,3-dichloro | hv | <u>85</u> | 76.4% |
| 57 | 2,3-dichloro | dark | <u>84</u> | 70-80% |
| 58 | 2,5-dibromo | hv | <u>87</u> | 85-90% |
| 59 | 2,5-dibromo | dark | <u>86</u> <u>87</u> | 60% 3% |
| Ref. 31 | 2,6-dibromo | hv | | 89% |

a

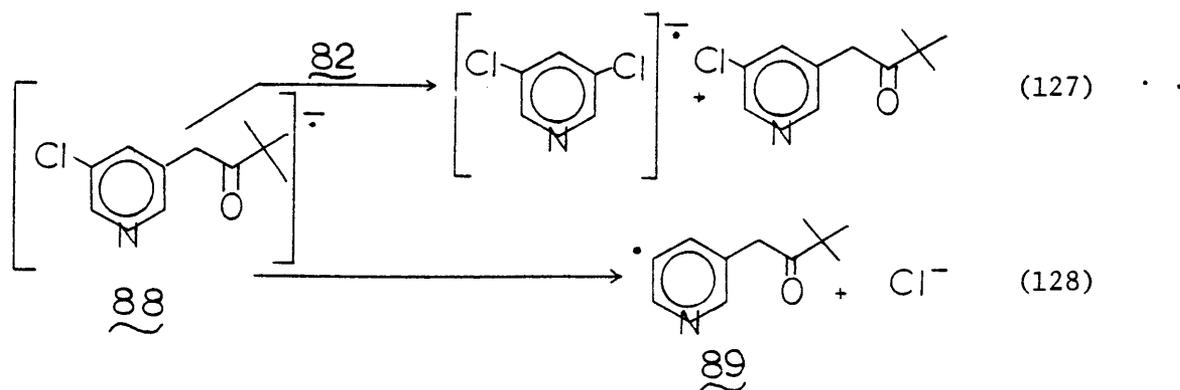
Reaction time 15 min.

b Ratio of enolate to substrate 7.25:1

c 20 mol % of DTBN used as inhibitor

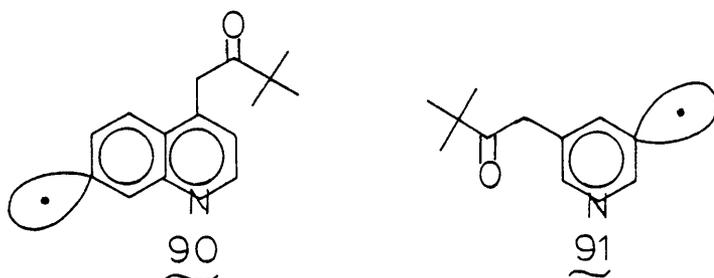
2,5-dibromopyridine with pinacolone enolate gave a 60% recovery of starting aromatic substrate and <3% yield of the disubstitution product 87.

It appears that although the spin density at the 3,5-position of pyridine radical anion is low, it is not low enough to slow the rate of decomposition of the radical anion of monosubstituted pyridine (88) to make the competitive electron transfer of an electron to a molecule of starting substrate (eq. 127) more favorable than fragmentation into the pyridinyl radical 89 and halide anion (eq. 128).



The electron transfer rate can be related to the difference in reduction potentials between the two reacting species. This difference is probably about the same between dichloroquinoline and the quinolinyl ketone couple vs the dichloropyridine and the pyridinyl ketone. So assuming this rate to be about the same, the monosubstituted pyridinyl ketone radical anion must decompose faster than the quinolinyl radical anion. The higher reduction potential of the pyridine is most likely responsible for this increased unimolecular decomposition rate (see Section IV).

An alternative view would be to rationalize the rate of decomposition as being dependent upon product stability rather than reactant stability. In the case of 4,7-dichloroquinoline the nitrogen in the pyridine portion of the quinoline ring would not have as much of an influence on the radical stability as in the pyridine case. The 7-quinoliny radical (90) is more of a phenyl radical in terms of stability than the pyridyl radical (91).



(See discussion in Section IV).

It should be noted that the yield in cases involving the 3-substituted pyridines is lower than in cases involving the 2- or 4-positions of the ring. One explanation of this decreased yield could be the spin density problem mentioned above. How this could effect the amount of polysubstitution on the enolate will be discussed.

An assumption implicit in the radical chain $S_{RN}1$ reaction is that when the electron that initiates the reduction of the aromatic substrate comes from the enolate, the resulting radical's and radical anion's lifetimes are long enough for the two species to diffuse away from each other. If they did not, the radical anion would decompose to aromatic radical and halide anion while still in the presence of the oxidized enolate. A chain termination step would

then take place with the coupling of the two radicals, and if this occurred exclusively there would be no chain reaction. Evidently this is not the case since chain activity is observed in most aromatic systems studied. But, we must consider a related possibility in the propagation step and its consequences.

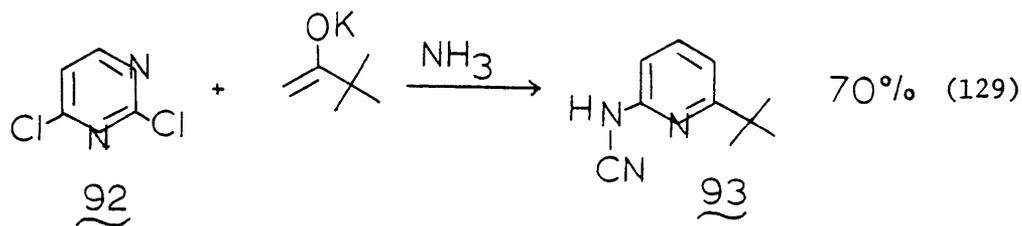
When the enolate and the aromatic radical combine to form the radical anion of the product, then an electron transfer to an aromatic substrate must take place. Once this happens the radical anion (of the substrate) and the neutral product molecule diffuse away from each other. If the radical anion decomposes rapidly to produce the aromatic radical, chances of reaction taking place are small since both species are uncharged. In the presence of excess enolates the radical combining with an enolate rich with electrons is more likely.

In the case of a long-lived radical anion, the life-time may be long enough so that the neutral product molecule could be ionized by the stronger base of the enolate. If this did occur faster than the nucleofuge left the aromatic ring, then the close proximity of the product anion to the radical when formed would increase the anion's effective concentration. Coupling would take place and the poly-substituted (two aromatic rings) product would be the final result.

3. Pyrimidine

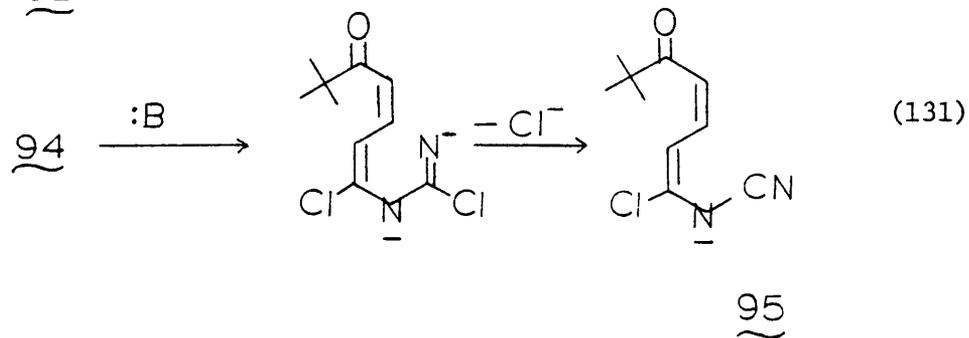
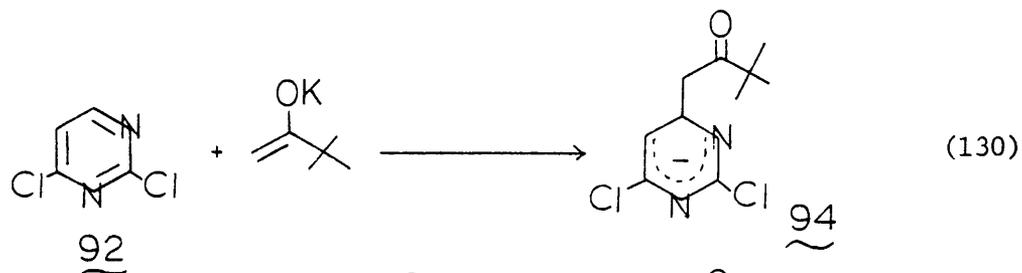
In the case of the 2,4-dichloropyrimidine, the competing S_N ANRORC mechanism proceeds at a much faster rate than the $S_{RN}1$ or any

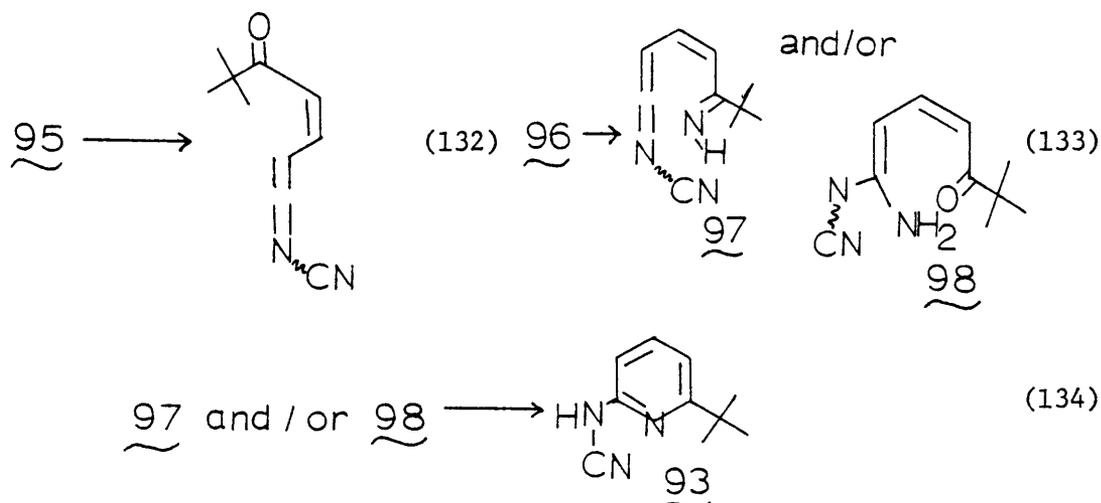
type of S_NAR mechanism. Reaction of pinacolone enolate with 2,4-dichloropyrimidine (92) in the dark gave, after chromatographic workup on silica gel, 70% of N-(6-t-butylpyridin-2-yl)cyanamide (93) (eq. 129). Photostimulation of this reaction failed to



produce any change in the course of the reaction. The same results were also obtained under inhibited conditions with DTBN as inhibitor.

These results may be explained by the well known $S_NANRORC$ mechanism. Initial attack of the nucleophile at the unhindered 6-position of the pyrimidine ring leads to the resonance stabilized anion 94 (eq. 130). Additional base then causes the ring opening of

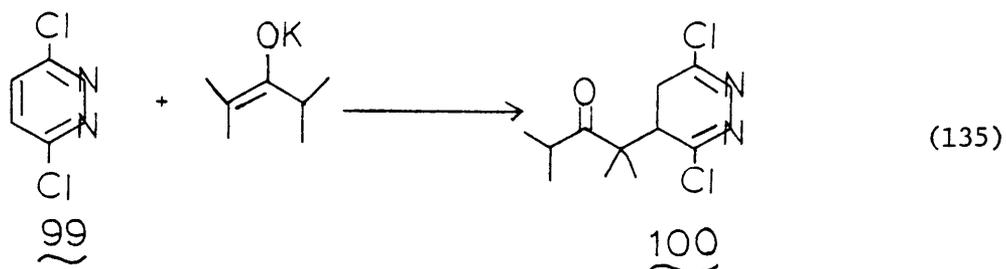




the pyrimidine with loss of chloride ion from the 2-position to give the intermediate 95 (eq. 131). The intermediate 95 may then undergo expulsion of the chloride from what was the 4-position of pyrimidine. Alternatively, 95 could possibly not lose the chloride until after protonation upon quenching. By whatever route, 96 is a likely intermediate (eq. 132). Nucleophilic attack by ammonia at the 4-position would give 98, or as an alternative, ammonia could form the imine at the carbonyl carbon to give 97 (eq. 133). This reaction most likely takes place during the evaporation of the ammonia from the reaction. Either or both of intermediates 97 or 98 could be responsible for the ring-closed product 93 (eq. 134).

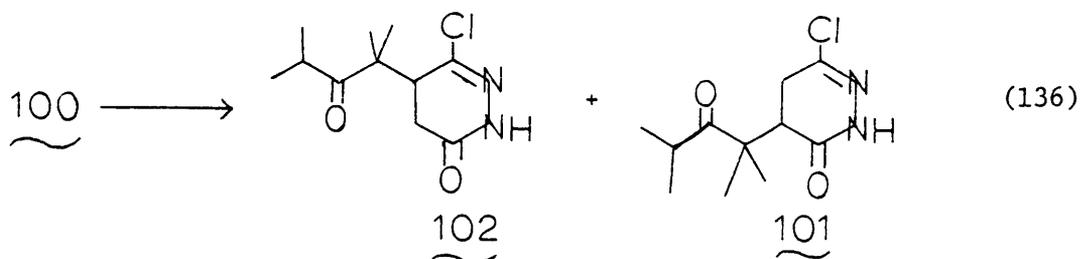
4. Pyridazine

Reaction of 3,6-dichloropyridazine (99) with diisopropyl ketone enolate under photostimulation, dark, or inhibited conditions produced high yield of the unstable addition product 100 (eq. 135). This



product tends to decompose rapidly upon heating and is almost completely decomposed after 8 hrs at room temperature.

The addition product 100 can be hydrolyzed by wet silica gel to dihydropyridazinones 101 and 102 (eq. 136).



The hydrolysis apparently removes only one chlorine substituent from 100, since the isolated compounds 101 and 102 are resistant to further hydrolysis.

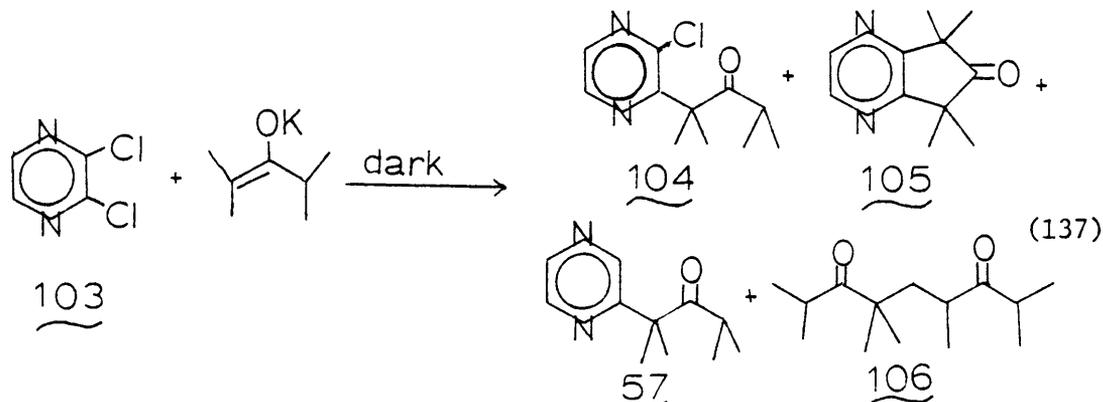
Reaction of 3,6-dichloropyridazine with either acetone or pinacolone enolates resulted in isolation of only red tars. These tars were reminiscent of the decomposition of 100 into tar.

The replacement of the methoxy group in 3-chloro-6-methoxypyridazine by the chlorine substituent resulted in a decrease in substitution (none detected) and an increase in the amount of addition product at the 4-position. The increased π -deficiency in the dihalopyridazine should cause an increase in both the substitution process and the

addition reaction; however, from these results it appears that the addition reaction is accelerated in rate more than the $S_{RN}1$ or other types of substitution processes.

5. Pyrazine

Both 2,3-dichloro and 2,6-dichloropyrazine under facile substitutions in the dark with ketone enolates. These results are listed in Table XII. When 2,3-dichloropyrazine (103) reacted with diisopropyl ketone enolate in the dark, several products were isolated. These were the chloro-monosubstituted pyrazine 104 (17%), the unsymmetrical dimer 106 (5%), the pyrazinylcyclopentanone 105 (6.2%), and pyrazinyldiisopropyl ketone 57 (2.3%) (eq. 137).



Under inhibited conditions (15 mol % of DTBN) in the dark, the product ratio in this reaction was not changed appreciably. The yields in this experiment (expt. 48, Table XII) of 104, 105, 106, and 57 were 21.5%, 6.5%, 1.4%, and 0%, respectively.

Table XII

Reaction of Dihalopyrazines with Ketone Enolates

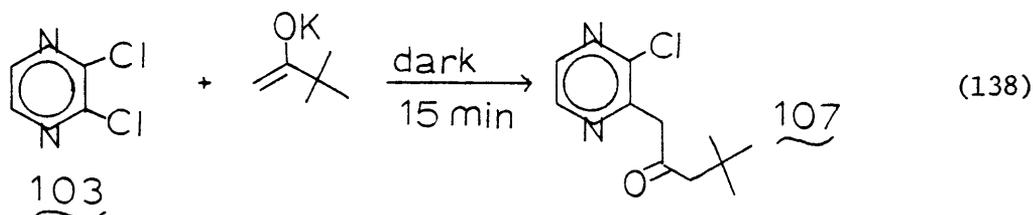
| Expt. No. | Pyrazine | Ketone | Conditions ^{a,b} | Product No. | Yield |
|-----------|--------------|--------------------|------------------------------|-------------|-------|
| 47 | 2,3-dichloro | diisopropyl-ketone | dark | <u>104</u> | 17% |
| | | | | <u>105</u> | 6.2% |
| | | | | <u>57</u> | 2.3% |
| | | | | <u>106</u> | 5% |
| 48 | 2,3-dichloro | diisopropyl-ketone | dark; inhibited ^c | <u>104</u> | 21.5% |
| | | | | <u>105</u> | 6.5% |
| | | | | <u>57</u> | 0% |
| | | | | <u>106</u> | 1.4% |
| 49 | 2,3-dichloro | pinacolone | dark | <u>107</u> | 71% |
| 50 | 2,3-dichloro | pinacolone | dark; inhibited ^c | <u>107</u> | 70% |
| 51 | 2,6-dichloro | pinacolone | dark | <u>109</u> | 99% |
| 52 | 2,6-dichloro | pinacolone | dark; inhibited ^c | <u>109</u> | 98% |

^aReaction time 15 min.

^bRatio of enolate to substrate, 3.75:1

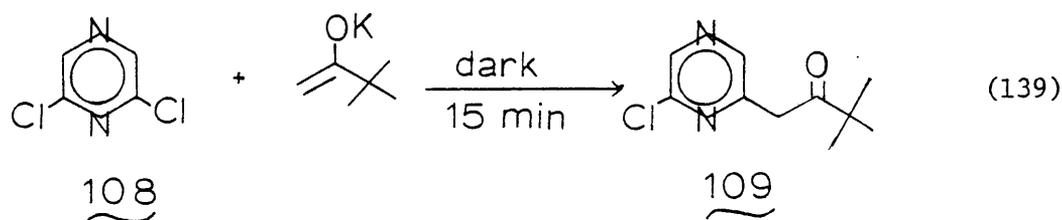
^c15 mol% of DTBN used as inhibitor

Pinacolone enolate in a 15 min reaction in the dark with 2,3-dichloropyrazine affords a 71% isolated yield of the monosubstitution product 107 (eq. 138). The remainder of the reaction



material balance was a red tar which proved chromatographically intractable. In an inhibited experiment (expt. 50, Table XII), no decrease in the yield of monosubstitution product 107 was found.

Using an isomeric dihalopyrazine, 2,6-dichloropyrazine (108) with pinacolone enolate resulted in excellent overall yield of monosubstitution product 109 (eq. 139).



Under radical inhibiting conditions (15 mol % of DTBN) no decrease in the yield of 109 was found.

From these reactions of dichloropyrazines, we find the same trend in reaction as was found for the other aromatic diazines; that is, addition reactions become more predominante over $S_{RN}1$ mechanism reactions than in the monochlorodiazines. Formation of monosubstitution products plus the lack of inhibition by DTBN in these equations

both point to an addition-elimination mode of substitution in dichloropyrazines. This is in harmony with the pyrimidine and pyridazine cases in which only ionic reactions with these ketone enolates were found.

VII. Conclusions

To gain a measure of the relative ease with which we can predict a given aromatic molecule will undergo the $S_{RN}1$ mechanism, comparison of the reduction potential of the parent heterocycle with other known systems that have had their $S_{RN}1$ activity and reduction potential gauged can give a measure of its $S_{RN}1$ feasibility and/or condition of reaction. The rationale for this correlation was discussed previously (See Section IV and V). A summary of this correlation is given in Table XIII.

From the Table it can be seen that decreasing the reduction potential (less negative values) of the heterocycle leads to a $S_{RN}1$ reaction that requires less stimulation. Heterocycles that have reduction potentials below that of quinoline proceeded to undergo the $S_{RN}1$ mechanism without photostimulation, and this is an indication of their "easy" reduction by the ketone nucleophile. There is a fairly smooth transition from reactions requiring photostimulation to those that proceed easily in the dark.

The line of demarcation in the thermal electron transfer with simple ketone enolates appears to be around -1.60 V vs the Hg pool in DMF for the parent heterocycle. At this point the activation energy necessary for electron transfer to the aromatic substrate is supplied by thermal processes. In the case of pyridazine and quinoline, this is a slow process; so photostimulation speeds substitution by supplying more initiations for the radical process.

Table XIII

Comparison of Electrochemical Reduction Potentials of
Unsubstituted Heterocycles and $S_{RN}1$ Reactivity

| Heterocycle | Reduction Potential in V vs Hg pool in DMF | $S_{RN}1$ Stimulation Requirement |
|-------------|---|--------------------------------------|
| Pyridine | -2.15 | hv |
| Pyrimidine | -1.78 | hv |
| Pyridazine | -1.61 | dark/hv |
| Quinoline | -1.59 | dark/hv |
| Pyrazine | -1.57 | dark |
| s-Triazine | -1.47 | - |
| Phthalazine | -1.41 | - |
| Quinazoline | -1.22 | $S_{N}AR$ |
| Quinoxaline | -1.09 | dark |
| Cinnoline | -1.06 | - |
| as-Triazine | -1.04 | - |

| Heterocycle | $S_{RN}1$ Process vs Purely Ionic Additions with Ketone Enolates | |
|---------------------------------|---|--------------|
| 2,3, or 4-bromopyridine | 95:5 | (hv) |
| 2-chloropyrimidine | 15:85 | (hv) |
| 4-chloro-2,6-dimethylpyrimidine | 99:0 | (hv) |
| 3-chloro-6-methoxypyridazine | 80:20 (hv) | 50:50 (dark) |
| 2-chloroquinoline | 95:5 (hv) | |
| 2-chloropyrazine | 98:2 (dark) | |
| 4-chloroquinazoline | 0:99 (dark) | |
| 2-chloroquinoxaline | 70:30 (dark) | |

It is tempting to draw a correlation between one-electron reduction potentials and ionic addition processes. However, it can be seen that the quinoxaline substrate with a very low reduction potential is not prone to ionic addition but is very active in radical anion type processes. The electrochemical data is valid only for one-electron transfer processes and does not correlate well with ionic additions.

From the data presented herein, the $S_{RN}1$ reaction is a viable substitution mechanism when one of the following conditions are met:

- 1) the reduction potential of the substrate is low enough so that enough initiations are made to make the overall rate favorable over ionic addition mechanisms
- 2) ionic additions are slow or reversible so that alternative radical mechanisms can compete.

These conditions are illustrated by the reaction of 2-chloropyrimidine.

The $S_{RN}1$ reaction proceeds very well when the competing ionic addition process does not siphon the 2-chloropyrimidine into what appears to be ring-opened products. With tertiary enolates addition to the 4-position of the ring appears to be reversible (expt. 5-7). Primary enolates that can add and undergo further ionization remove the aromatic substrate by an irreversible ring opening. This does not happen to tertiary enolates, and overall substitution via a $S_{RN}1$ process occurs in good yield.

In the case of 3-chloro-6-methoxyimidazole substitution via a $S_{RN}1$ mechanism occurred in the dark, but an ionic addition was competitive with some ketone enolates. This result can be compared to

that of 2-chloropyrimidine. This pyrimidine is more reactive to ionic addition (Table IV) than 3-chloropyridazines, and that coupled with the lower reduction potential of the pyridazine enables the $S_{RN}1$ mechanism to compete with ionic addition in substituted pyridazines.

From the reduction potentials in Table XIII, we would expect that 2-chloroquinoline would be more reactive than 3-chloro-6-methoxypyridazine. However, the electron donating ability of the methoxy substituent in pyridazine probably increases the reduction potential of that substrate,¹²⁷ thereby making the $S_{RN}1$ more difficult to initiate. So, 2-chloroquinoline has a reactivity towards certain enolates that does not fit the expected correlation. However, with diisopropyl ketone enolate, 2-chloroquinoline displayed a reactivity in the dark that 3-chloro-6-methoxypyridazine did not approach. The possible explanations for this behavior are detailed in Section VI. B.

In the case of quinazoline although the reduction potential indicates that electron transfer should be relatively facile, the stability of the σ -complex (110) in a S_NAR mechanism speeds that pathway toward substitution (diagram IV). This complex (110) should be contrasted in stability to that of 111 where resonance forms (VB) cannot be drawn that localize the negative charge directly onto the 4-position of quinoxaline. This surely decreases the stability of the complex 111 as opposed to that of 110.

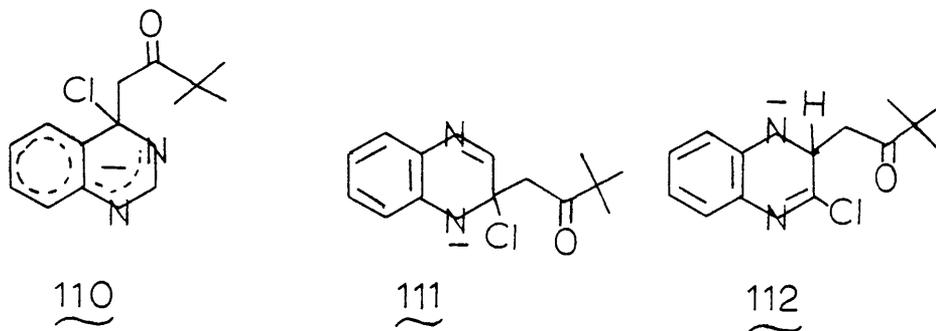


Diagram IV

The steric requirement that a S_NAR pathway demands is illustrated by the ionic addition mode of reaction in chloroquinoline. Pinacolone enolate adds to the 3-position to give intermediate 112 rather than addition at C-2 to give 111. Also, the chlorine substituent can stabilize the anion in 112 more effectively than in 111 by delocalization of charge to C-2.

The competition of addition vs substitution via $S_{RN}1$ or S_NAR is very pronounced in going from the monohalodiazines to the dihalodiazines. For example, the pyrazine series completely lost its $S_{RN}1$ activity by adding an addition chlorine to chloropyrazine. This is probably due to the added stability the second chloride inductively lends to the addition compounds.

In the case of the dichloropyridines the S_NAR mode of substitution was enhanced (see dark reactions), but the presence of only one aza activation decreases the rate of ionic addition relative to the other aromatic diazines. For this reason the $S_{RN}1$ mechanism can compete favorably in a photostimulated substitution process.

These reactions illustrate and define the presence of the previously unrecognized $S_{RN}1$ pathway in aromatic diazines. The conditions and viability of this mechanism were shown to be related to the electrode reduction potentials of the parent aromatic system.

EXPERIMENTAL

All reactions were conducted under an atmosphere of nitrogen; quenching and work-up of the resulting products were performed under atmospheric conditions unless otherwise noted. All photostimulated reactions were conducted in a Rayonet RPR-240 photochemical reactor. Gas chromatographic analyses and separations were accomplished on Varian Associates 90-P or 1200 instruments using various columns of Carbowax 20M on Chromosorb supports. The following columns were used for both GLC preparative work and analysis of the crude mixtures:

- 1) 7' X 1/4" aluminum column packed with Chromosorb G-HP with 2% Carbowax 20M
- 2) 6' x 1/4" aluminum column packed with Chromosorb G-HP with 2% Carbowax 20M
- 3) 4' x 1/4" aluminum column packed with Chromosorb W with 10% Carbowax 20M
- 4) 6' x 1/4" aluminum column packed with Chromosorb Z with 2% Carbowax 20M
- 5) 5' x 1/4" aluminum column packed with Chromosorb Z with 2.15% Carbowax 20M.

All flow rates of helium for GLC analysis were between 50-60 ml/min. Determinations of yield by GC analysis used benzoate esters as internal standards. ^1H NMR spectra were determined on a JOEL JMN-PS-100 or Varian EM-390 spectrometer at 100 MHz or 90 MHz, respectively, using tetramethylsilane as internal reference. Mass spectra were determined by Douglas S. Shearer or attempted by Jorge I. Bedia on a Hitachi

Perkin-Elmer RMU-6E mass spectrometer. Infrared spectra were produced on a Beckman IR-20A-X spectrophotometer. Elemental microanalyses were attempted by Jorge I. Bedia on a Perkin-Elmer 240 elemental analyzer or satisfactorily performed by Galbraith Laboratories, Knoxville, Tennessee. Melting points were observed in a Thomas-Hoover apparatus and are uncorrected.

All solvents were of commercial quality except for those purified as noted.

Liquid chromatographic separations were performed on silica gel. Preparative TLC plates were made from EM Merck PF-254 type 60 Silica Gel. Analytical TLC plates were carried out on Eastman 13181 Silica Gel with fluorescent indicator (no. 6060) with polymer backing. Other less active separations were carried out on Merck HF-254 (type 60) Silica Gel (cat. 7739) mechanically spread on microscope slide glass plates. Column chromatography was adequately accomplished using a low pressure column and reservoir under 10-25 lbs of nitrogen pressure with Woelm 126 silica gel ($<.063$ mm). For a typical reaction a column packing of 2.2 x 20 cm was used with fractions taken every 30 ml. The solvent used was adjusted so that the desired component had a Rf of 0.3. The fractions were detected by TLC.

Reaction of the various heteroaromatic compounds was carried out in one of the following procedures. Exceptions to these general procedures as well as colors of the reactions at various stages will be noted for each individual reaction. Liquid ammonia was a commercial anhydrous quality.

Procedure A: For the photostimulated reactions, 150-175 ml of anhydrous ammonia was introduced directly into a cylindrical dewar flask (unsilvered) that measured 51.0 x 3.5 cm (I.D.) topped with a single 35/40 F ground glass joint. This joint was fitted, prior to ammonia introduction, with an adapter containing three 24/40 F male ground glass joints. These were fitted with stoppers, addition funnel, or dry-ice condensers as needed. (Short reaction times < 30 min do not require the condenser, since loss of ammonia in the insulated flask is negligible.) With positive nitrogen pressure 11.25 mmoles of potassium metal is dropped into the ammonia. Addition of a few mg of ferric nitrate hydrate facilitates amide formation. After amide formation is complete, an anhydrous ethereal solution of the carbon acid (11.25 mmol) is added dropwise (1 1/2 min, 7 ml, then 3 ml rinse). After mixing of the solutions is complete (magnetic stirring with bare metal magnet), the lights on the photochemical reactor are turned on (4 x 12.5 W florescent bulbs emitting maximally at 350 nm). Addition of the aromatic substrate (3.00 mmol) in 10 ml of ether is accomplished in 1 1/2 min. Irradiation for 15 min (total) gives a reaction mixture that is quenched by pouring the liquid ammonia solution directly onto solid ammonium chloride (3.5 g) contained in a 2 l beaker. The reaction vessel is washed twice with 100 ml of ether each, and the washes are combined with the ammonical solution. Evaporation of the ammonia is readily accomplished on a mildly warm hot plate wet with ethanol (to help transfer heat and prevent ice formation). Briefly boiling the ether removes residual

ammonia, and filtration of the ethereal solution from the solid salts is readily performed. Crushing the salts with a spatula and four titrations with 50 ml each of ether gives good extraction in most cases. Evaporation of the ether gives crude product.

Procedure B: In a 250 ml 3-neck 24/40 S RB flask fitted with two nitrogen bubblers and an additional funnel, is added 150-175 ml of anhydrous liquid ammonia run in directly from the tank via a tygon tube. 11.25 mmol of potassium amide is generated as described in procedure A; then addition of the carbon acid (11.25 mmol) in 7-10 ml of ether is done. Before the aromatic substrate is added (3.00 mmol in 10 ml ether), the flask is carefully wrapped with several layers of black cloth and lights are extinguished. Quenching the ammoniacal solution, rinsing the reaction vessel, evaporation of the ammonia, and extraction of the salts is identical to that described in procedure A. Evaporation of the ether gives the crude product.

Experiment 1. Photostimulated Reaction of Acetone Enolate and 2-Chloropyrimidine (21).

Procedure A was used to produce a bright red solution at the end of the irradiation period. This solution was quenched to a very bright orange ammoniacal solution that faded to a darker red upon evaporation of the ammonia. Kugelrohr distillation of the crude product at 100°C (0.1 torr) gave a red oil which was > 90% 1-(pyrimidin-2-yl)propan-2-one (22). Purification of this oil by preparative GLC on column I (170°C, retention time 20 min) gave an

analytical sample as a yellow oil: IR (neat) 3040 w (C-H), 1715 s (C=O), 1640 m, 1560 s (pyr.),¹²⁹ δ 1430 s (pyr.); ¹H NMR (CDCl₃) 2.10 (s, .6 H, CH₃), 2.28 (s, 2.4 H, CH₃), 4.13 (s, 1.6 H, CH₂), 5.45 (s, .2 H, enol CH), 6.90 (s, .2 H, 5 H pyr.),¹³⁰ 7.20 (t, .8H, 5H pyr.), 8.50 (d, .4H, 4.6H pyr.), 8.68 (d, 1.6H, 4.6H pyr.), 13.40 (broad s, .2H, enol O-H). Anal. calcd for C₇H₈N₂O: C, 61.75; H, 5.92; N, 20.57. Found: C, 59.68; H, 6.86; N, 15.84.

GLC analysis of the crude mixture using 2-aminopyrimidine¹³¹ (23) as internal standard gives a 15% yield of (22) and 4.4% of (23). The remainder of the crude product is an intractable tar soluble in polar solvents.

Experiment 2. Dark Reaction of Acetone Enolate and 2-Chloropyrimidine (21).

Procedure B resulted in no detectable amounts of substitution product (22) by GLC. A 5.2% yield of 2-aminopyrimidine (23) was detected from GLC data. The remainder of the reaction was the dark red tar similar to the tar found in Experiment 1.

Experiment 3. Inhibited Photostimulated Reaction of Acetone Enolate and 2-Chloropyrimidine (21).

Procedure A was followed except that 43.2 mg (10 mol %) of di-t-butylnitroxide was added to the aromatic halide before addition to the enolate. This gave identical products that experiment 2 produced.

Experiment 4. Photostimulated Reaction of Pinacolone Enolate and 2-Chloropyrimidine (21).

Procedure A gave a red solution that produced after Kugelrohr distillation (90°C; .07 torr) 32% of 1-(pyrimidin-2-yl)-3,3-dimethylbutan-2-one (24) and ~4% of 2-aminopyrimidine (23). An analytical sample of 24 was obtained by preparative GLC on Column I (180°C, retention time 13 min) as a pale yellow oil. IR (neat) 3040 w (C-H), 1705 s (C=O), 1625 s, 1575 s, 1560 s, 1540 s (pyr.), 1430 s (pyr.); ¹H NMR (CDCl₃) δ 1.24 (s, 9H, t-Bu), 4.17 (s, 1.3H, CH₂), 5.66 (s, .35H, enol), 6.87 (t, 5Hz, .35H, 5H pyr.), 7.12 (t, 5Hz, .65H, 5H pyr.), 8.46 (d, 5Hz, .70H, 4,6H pyr.), 8.63 (d, 5Hz, 1.30H, 4,6-H pyr.), 13.80 (broad singlet, .35H, enol). Anal. calcd for C₁₀H₁₄N₂O: C, 67.39; H, 7.92; N, 15.72. Found: C, 66.22; H, 7.72; N, 15.46.

The remainder of the reaction was an intractable red tar that was similar to the tar formed in experiment 1.

Experiment 5. Photostimulated Reaction of Diisopropyl Ketone Enolate and 2-Chloropyrimidine (21).

Procedure A was followed to give a slightly yellow ethereal solution. Evaporation of the solvent and Kugelrohr distillation gives by GLC analysis 88.5% of 2-(2-pyrimidinyl)-2,4-dimethyl-3-pentanone (25) and 4.3% of 2-aminopyrimidine (23). Also detected in the crude mixture was the unsymmetrical dimer (27) and pyrimidine (26), both in yields < 1/2% and with spectra identical to authentic samples.

Spectral data for 25 gave the following: IR (neat) 3030 w (C-H), 1710 s (C=O) 1670 s, 1660 s, 1415 s (pyr.). ^1H NMR (CDCl_3) δ 1.02 (d, 7Hz, 6H, iso-propyl), 1.58 (s, 6H, CH_3), 2.63 (septet, 7Hz, 1H, iso-propyl), 7.17 (t, 5Hz, 1H, 5H pyr.), 8.68 (d, 5Hz, 2H, 4,6 pyr.). Anal. calcd for $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}$: C, 68.70; H, 8.40; N, 14.57. Found: C, 68.92; H, 8.70; N, 14.47. GLC analysis was done on column I (165°C, retention time of 25, 22.5 min).

Experiment 6. Dark Reaction of Diisopropyl Ketone Enolate and 2-Chloropyrimidine (21).

Procedure B gave an almost colorless oil that by GLC indicated a 50% recovery of 2-chloropyrimidine, 7.5% of 2-aminopyrimidine, and no detectable trace of the substitution product, 25. Also isolated by preparative GLC on column IV (170°C and retention time 10.5 min) was 2-(2-chloropyrimidin-4-yl)-2,4-dimethyl-2-pentanone, 28, in 17% yield, mp, 54-58°C. Spectral data on 28 gave the following: IR (solid) 3080 w (C-H), 1705 s (C=O), 1575 s (pyr.), 1538 s (pyr.); ^1H NMR (CDCl_3) δ 1.00 (d, 7Hz, 6H, iso-prop.), 1.56 (s, 6H, $(\text{CH}_3)_2$), 2.74 (septet, 7Hz, 1H, iso-prop.), 7.2H (d, 5Hz, 1H, 5-pyr.), 8.62 (d, 5Hz, 1H, 6-pyr.). Anal. calcd for $\text{C}_{11}\text{H}_{15}\text{ClN}_2\text{O}$: C, 58.28; H, 6.67; N, 12.36; Cl, 15.64. Found: C, 58.50; H, 7.01; N, 12.09.

Experiment 7. Inhibited Photostimulated Reaction of Diisopropyl Ketone Enolate and 2-Chloropyrimidine (21).

Following procedure A except with .07 g of di-t-butyl nitroxide added to the aromatic substrate, the crude product gave by GLC analysis,

58% recovery of 2-chloropyrimidine, 6.8% of 2-aminopyrimidine (23), and 15% of the 4-substituted pyrimidine (28).

Experiment 8. Reaction of Potassium t-butoxide with 2-Chloropyrimidine.

By procedure B complete consumption of the 2-chloropyrimidine was accomplished. The only isolated product was 2-pyrimidinyl-t-butyl ether (113) by preparative GLC on column I (150°C, retention time of 2.8 min). Spectral data gives: IR (neat) 3035 w (C-H), 1577 s, 1555 s, 1415 s (pyrimidine), 1170 s (C-O). ¹H NMR (CDCl₃) δ 1.63 (s, 9H, t-Bu), 6.82 (t, 5Hz, 1H, 5H pyr.), 8.40 (d, 5Hz, 2H, 4,6-pyr.). Anal. calcd for C₈H₁₂N₂O: C, 63.13; H, 7.95; N, 18.41. Found: C, 62.84; H, 7.82; N, 18.25.

Experiment 9. Inhibited Reaction of Potassium-t-butoxide with 2-Chloropyrimidine (21).

Addition of 20 mol % of di-t-butylnitroxide to the aromatic halide in procedure B gives a crude product that by GLC analysis (same conditions as experiment 8) indicated a 5:1 ratio of substitution product (113) to 2-chloropyrimidine (21).

Experiment 10. Photostimulated Reaction of Pinacolone Enolate and 4-Chloro-2,6-dimethoxypyrimidine (29)¹³¹

Under procedure A conditions the almost colorless crude product was GLC analyzed with benzylbenzoate as internal standard on column III (200°C, retention time of 16 min). This was shown to be 1-(2,6-dimethoxypyrimidin-4-yl)-3,3-dimethylbutan-2-one (30). IR

(neat) 3020 w (C-H), 1705 s (C=O), 1635 s, 1595 s, 1560 s, 1540 s, 1385 s, 1350 s (pyrimidine), 1095 s (C-O), 1057 s (C-O). ¹H NMR (CDCl₃) δ 1.19 (s, 9H, t-Bu), 3.88 (s, 2H, CH₂), 3.94 (s, 6H, (OMe)₂), 6.28 (s, 1H, 5-pyr.). Anal. calcd for C₁₂H₁₈N₂O₃: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.39, H, 7.85; N, 11.68.

A small trace of starting material (29) was noted in GLC trace (< 1%).

Experiment 11. Dark Reaction of Pinacolone Enolate and 4-Chloro-2,6-dimethoxypyrimidine (29).

Procedure B resulted in a 80% recovery of the aromatic substrate (29) and no trace of the substitution product (30).

Experiment 12. Inhibited Photostimulated Reaction of Pinacolone Enolate and 4-Chloro-2,6-dimethoxypyrimidine (29).

Procedure A modified by adding .085 g (20 mol %) of di-t-butyl nitroxide (DTBN) to the aromatic chloride resulted in GLC analysis (under the same conditions as Experiment 10) of 6% substitution product (30) and a 65% recovery of the aromatic halide (29).

Experiment 13. Photostimulated Reactions of Pinacolone Enolate and 3-Chloro-6-Methoxy pyridazine (47).

Procedure A gives a dark yellow solution that can be chromatographed (flash) with 25:75 ether: hexane to give 1-(6-methoxy pyridazi-3-yl)-3,3-dimethylbutan-2-one (50) as a low melting yellow-red solid (m.p. 46-9°C) in 72% yield by GLC analysis column I (220°C, retention

time 13.5 mins). I.R. (solid) 3035 w (C-H), 1707 s (C=O), 1595 m, 1555 m, 1470 s, 1420 s, 1305 s (pyridazine) 1060 s, 1015 (C-O).
 ^1H NMR (CDCl_3): δ 1.21 (s, 9H, t-Bu), 4.06 (s, 3H, OCH_3), 4.08 (s, 2H, CH_2) 6.86 (d, 9Hz, 1H, ring H), 7.27 (d, 9Hz, 1H, ring H).
Anal. calcd for $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.07; H, 7.81; N, 13.52.

A trace of aromatic chloride starting material (47) was detected (< 5%).

Experiment 14. Dark Reaction of Pinacolone Enolate and 3-Chloro-6-methoxypyridazine (47).

Procedure B yields a solution (red) that by GLC analysis, with conditions described in Experiment 13, indicate a 38% yield of substitution product (50) and 24% isolated yield of starting material (47).

Experiment 15. Inhibited Dark Reaction of Pinacolone Enolate and 3-Chloro-6-Methoxypyridazine (47).

Procedure B, with the modification of adding .043 g of DTBN (10 mol %) to the pyridazine before addition to the enolate, resulted in a 70% recovery of starting material (47) by GLC analysis described in experiment 13. No trace of substitution product (50) was detected.

Experiment 16. Photostimulated Reaction of Diisopropylketone Enolate and 3-Chloro-6-Methoxypyridazine (47).

Procedure A gives a yellow ethereal solution that darkens slowly upon standing or rapidly with heating. GLC analysis with dimethyl-

phtalate as internal standard on column I (215°C, retention time 11.25 min) gave a peak identified as 2-(6-methoxypyridazin-3-yl)-2,4-dimethylpentan-3-one (48) in 13.3% yield. Also recovered in 50% yield is 3-chloro-6-methoxypyridazine. 48 gave spectral data as follows: IR (neat) 3080 w (C-H), 1715 s (C=O), 1600 m, 1-50 w, 1475 s, 1420 s, 1310 s (pyridazine), 1040 m, 1015 s (C-H). ¹H NMR (CDCl₃) δ 0.92 (d, 7Hz, 6H, iso-prop.), 1.61 (s, 6H, (CH₃)₂), 2.85 (septet, 7Hz, 1H, iso-prop.), 4.10 (s, 3H, OCH₃), 6.87 (d, 9Hz, 1H, pyrada.), 7.22 (d, 9Hz, 1H, pyrada.). Anal. calcd for C₁₂H₁₈N₂O₂: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.58; H, 7.94; N, 12.56.

Lengthening the irradiation time to 1.00 hr resulted in a 17-20% yield of substitution product (48) and 15% yield of starting material (47). The remainder of the reaction material was a strongly absorbed (on silica gel) material that darkened upon contact with silica gel or heat.

Experiment 17. Dark Reaction of Diisopropyl Ketone Enolate and 3-Chloro-6-methoxypyridazine (47).

Procedure B yields a colorless solution that upon evaporation of ether crystallizes into slightly impure starting material (47). Longer reaction times (1 hr) give ethereal solutions which after stirring with wet silica gel for 2 days gave a 8.3% yield of 2-(4,5-dihydro-6-methoxypyridazin-3-one-4-yl)-2,4-dimethylpentan-3-one (49). Purification of 49 was accomplished by developing the crude mixture on preparative layer chromatography (PLC) silica gel with 50:50 ether:hexane. IR (solid) 3250 m (broad, N-H), 1705 s (C=O) 1660 s (C=O),

1475 m, 1345 s (pyridazine), 1005 s (C=O). ^1H NMR (CDCl_3) δ 1.08 (d, 7Hz, 6H, iso-propyl), 1.20 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 3.08 (septet, 1H, 7Hz, iso-propyl), 2.45 and 2.52 (ABX, $J_{\text{AB}} = 17\text{Hz}$, 2H, CH_2), 3.32 (ABX, $J_{\text{AX}} = J_{\text{BX}} = 8\text{Hz}$, 1H, C-4 pyr. H), 3.65 (s, 3H, OCH_3), 8.50 (broad s, 1H, NH). Anal. calcd for $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_3$: C, 59.98; H, 8.39; N, 11.66. Found: C, 59.95; H, 8.41; N, 11.63.

The remainder of the reaction material was recovered 47.

Experiment 18. Dark Reaction of Acetone Enolate and 3-Chloro-6-Methoxy pyridazine (47)

Procedure B yields a red oil that by Kugelrohr distillation at 110° (.1 torr) gave a yellow oil. Preparative GLC and analysis on column IV (153°C , retention time 10.0 mn) gave a yellow oil. This oil was identified as 1-(6-methoxy pyridazin-3-yl)-2-propanone (51). IR (neat) 3080 (w) (C-H), 1705 s (C=O). ^1H NMR (CDCl_3) δ 2.30 (s, 3H, CH_3), 4.03 (s, 2H, CH_2), 4.13 (s, 3H, OCH_3), 6.93 (d, 15 Hz, 1H, pyrida.), 7.29 (d, 15Hz, 1H, pyrida.). Anal. calcd for $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.60; H, 6.28; N, 16.75.

The remainder of the reaction was a very dark red tar that was elutable on column chromatography only with alcohol solvents.

Experiment 19. Dark Reaction of Acetone Enolate and Diisopropylketone Enolate with 3-Chloro-6-methoxy pyridazine (47).

Procedure B was modified so that the total enolate concentration was the same as in the previous experiment, but the acetone and diisopropyl ketone enolates were in equal concentration. GLC analysis

of the reaction, using dimethyl phthalate as internal standard and column conditions described in Experiments 17 and 18, indicated a 19.3% yield of acetone substitution product (51) and 21.2% yield of diisopropyl ketone substitution product (48).

Changing the enolate ratio in another reaction to 90:10 diisopropyl ketone acetone, resulted in a <5% yield of 51 and a 31.5% yield of 48.

Experiment 20. Dark Reactions of Acetone and Pinacolone Enolates with 2-Chloropyrazine (54).

Procedure B modified by shortening the reaction time to 5 min, gave a 98% of 1-(pyrazin-2-yl)-propan-2-one (56). Anal. calcd for $C_7H_8N_2O$: C, 61.75; H, 5.92. Found: C, 61.81; H, 6.08.^{128a,b}

Pinacolone reacted with 54 in a similar manner, but it required 10 min for the reaction to proceed to completion (Procedure B). Anal. calcd for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92. Found: C, 67.45; H, 7.88.^{128a,b}

Experiment 21. Dark Reaction of Diisopropyl Ketone Enolate and 2-Chloropyrazine (54).

Procedure B gives an almost colorless solution that by preparative GLC on column IV (165°C) gave a colorless oil of retention time 6.0 min. Using dimethyl phthalate as internal standard a 85% yield of 2-(pyrazinyl)-2,4-dimethylpentan-3-one (57) was determined. A 75.5% yield of 57 was isolated by Kugelrohr distillation. IR (neat) 3065 w, 3040 (C-H), 1710 s (C=O), 1570 w, 1520 w (pyrazine), 1035 s,

1015 s, 1000 s. ^1H NMR (CDCl_3) δ 0.94 (d, 7Hz, 6H, iso-propyl), 1.60 (s, 6H, $(\text{CH}_3)_2$), 2.72 (septet, 7Hz, 1H, iso-propyl), 8.55 (m, 3H, pyrazine). Anal. calcd for $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}$: C, 68.70; H, 8.40; N, 14.57. Found: C, 68.61; H, 8.26; N, 14.63.

A small amount of the unsymmetrical dimer (27) was noted (<1/2%). No detectable trace of pyrazine could be found.

Experiment 22. Dark Reaction of the Potassium Salt of Phenylacetonitrile and 2-Chloropyrazine (54).

Procedure B was followed to give a red solution in ammonia. This faded to a colorless solution when in ether. The crude product was recrystallized once from 2 ml of benzene diluted to 6 ml with hexane. A 78% isolated yield of analytically pure white crystals of phenylpyrazinylacetonitrile (58) was obtained (m.p. 132-133.5 $^\circ\text{C}$). Spectral characteristics and physical constants were identical to literature values.¹³² IR (solid) 3080 w, 3060 w, 3040 w (C-H), 2250 m (CN), 1600 w, 1520 w (phenyl), 1490 m, 1470 m, 1450 m, 1400 s, 1035 m, 1000 m. ^1H NMR (CDCl_3) δ 5.35 (s, 1H, CH), 7.37 (m, 5H, phenyl), 8.55 (s, 2H, pyraz.), 8.67 (s, 1H, pyraz.). Anal. calcd for $\text{C}_{12}\text{H}_9\text{N}_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.96; H, 4.46; N, 21.53.

Decreasing the reaction time to 3 min resulted in a 44% isolated yield of 58.

Experiment 23. Dark Inhibited Reaction of the Potassium Salt of Phenylacetonitrile and 2-Chloropyrazine (54).

Procedure B with 20 mol % of DTBN (.86g) added to 2-chloropyrazine resulted in a 38% isolated yield of the substitution product (58).

In a 3 min reaction with 20 mol % DTBN a 11% yield of 58 was isolated.

Also 10 mol % of p-dinitrobenzene was used as an inhibitor in a dark reaction. 77% yield of substitution product 58 was isolated.

Experiment 24. Dark Reaction of Acetophenone Enolate and 2-Chloropyrazine (54).

Procedure B gives a green solution from which a yellow solid, mp 95-96° C, was isolated in 60 % yield by recrystallization from benzene/hexane. IR (neat, crushed solid) 3050 w (C-H), 1705 s (C=O), 1650 s, 1605 m, 1475 s, 760 s, 740 s, 680 s. ¹H NMR (CDCl₃) δ 4.47 (s, 1.2H, CH₂), 6.18 (s, .4H, enol), 7.34 (m, 3H, aromatic), 7.75 (m, 1H, aromatic), 7.95 (m, 1H, aromatic), 8.15 (s, 1H, pyraz.), 8.40 (m, 2H, pyraz.), 13.77 (broad s, .4H, enol). Anal. calcd for C₁₂H₁₀N₂O: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.92; H, 5.10; N, 13.94. GLC analysis on column I (235° C retention time 16.8 mins) with benzylbenzoate as internal standard indicated a 82% yield of pyrazinylacetophenone (59).

Experiment 25. Inhibited Dark Reaction of Acetophenone Enolate and 2-Chloropyrazine (54).

Procedure B with 15 mol % of DTBN with 2-chloropyrazine resulted in no trace of 59 (substitution product) and a greater than 90% recovery of chloropyrazine.

Experiment 26. Dark Reaction of Pinacolone Enolate and 2-Chloroquinoxaline (60).

Procedure B gave a dark red ammonical solution that faded to light yellow in etheral solution. GLC analysis on column I (225° C) gave two products 62 and 61 in 15% and 70% yields, respectively. 61 was shown to be the direct substitution product, 1-(quinoxalin-2-yl)-3,3-dimethylbutan-2-one. IR (neat, solid) 3060 w (C-H), 1705 m (C=O), 1695 m, 1635 m, 1595 m, 1540 m, 1390 s, 1320 s, 1117 s, 1110 s, 760 s. ¹H NMR (CDCl₃) δ 1.23 (s, 9H, t-Bu), 4.16 (s, 1.33H, CH₂) 5.55 (s, .66H, enol), 7.23, 7.56, 7.89 (m, 4H, aromatic ring H), 8.12 (s, .66H, enol quinox. 3H) 8.59 (s, .33H, quinox. 3H) 14.0 (broad s, .66H, enol). mp 88-90° C (lit. 93.5° C¹³³) as yellow needles. Retention time was 19.7 min.

Compound 62 displayed a retention time of 16.4 min and was identified as 2-t-butylfuro[2,3-b]-quinoxaline¹³³ m p 95° C (lit. 143 mp, 98° C). Compound 62 was isolated as pale yellow needles from hexane in contrast to the colorless needles obtained by Hayashi.¹³³ IR (solid) 3080 w, 3060 w (C-H), 1621 w, 1580 m, 1565 m, 1390 m, 1380 s, 1320 m, 1305 s, 1075 s, 755 s. ¹H NMR (CDCl₃) δ 1.45 (s, 9H, t-Bu), 6.63 (s, 1H, 3H-furo), 7.61 (m, 2H, 6,7-ring), 8.02 (m, 2H, 5,8-ring).

When the reaction time was shortened to 3 min, the substitution product 61 was obtained in 70% yield, and 62 was obtained in 8.7% yield.

A reaction time of 1.0 min gave a 70% and 11.3% yield of 61 and 62, respectively.

Experiment 27. Inhibited Dark Reaction of Pinacolone Enolate and 2-Chloroquinoxaline (60).

Procedure B was modified by adding 90 mg (20 mol %) of DTBN to the 2-chloroquinoxaline before adding it to the enolate. Also, the reaction time was shortened to 3 min. GLC analysis under conditions described in Experiment 26 gave 38.1% of 61, the substitution product, and 18.1% of 62, the furoquinoxaline.

In a shorter reaction period of 1 min, the 20 mol % inhibited (DTBN) gave 26% and 26.6% of the substitution product 61 and 62, respectively.

Increasing the reaction period to 15 min and using 100 mol % (3.00 mmol, 432 mg) of DTBN, resulted in a 43.5% yield of 62, the furoquinoxaline. No trace of the substitution product 61 could be found by GLC analysis. Repeating the reaction and taking the crude product stripped of volatile products produced a red gum. This was dissolved in 150 ml of benzene and treated with 3.0 g of NiO₂ at reflux for 2 1/2 hrs. This procedure was an adaptation of that of Meyers.¹³⁴ Kugelrohr distillation of the crude product afforded a 58 % yield of the furoquinoxaline (62) (130° C, .15 torr). Recrystallization from hexane gave pale yellow needles m p 96°.

Experiment 28. Dark Reaction of Diisopropylketone Enolate and 2-Chloroquinoxaline (60).

Procedure B yields a blood red solution at the end of the reaction period that quenched to almost colorless light yellow solution. GLC

analysis and preparation on column I at 192° C gave three major components 63, 64, and 65 of retention time 7.5, 21.6, 28.6 min, respectively. The first peak (63) was identified as 2-isopropyl-quinoxaline.¹³⁵ IR (neat) (oil) 3060 w (C-H), 1495 m, 1463 m, 1090 m, 765 s. ¹H NMR (CDCl₃) δ 1.43 (d, 7Hz, 6H, iso-propyl), 3.30 (septet, 7Hz, 1H, iso-propyl), 7.64 (m, 2H, 6,7-H-quinox.), 7.96 (m, 2H, 5,8H-quinox.), 8.71 (s, H, 3H-quinox.). Anal. calcd for C₁₁H₁₂N₂: C, 76.71; H, 7.02; N, 16.26. Found: C, 76.57; H, 7.18; N, 16.45.

The second compound to be eluted, 64, was identified as 3,4-(quinoxalin-[b]-yl)-2,2,5,5-tetramethylcyclopentanone (mp 146-7° C) a white solid. IR (neat, solid) 3050 w (C-H), 1740 s (C=O), 1555 w, 1485 w, 1455 m, 1435 m, 1160 m, 1100 m, 755 s. ¹H NMR (CDCl₃) δ 1.50 (s, 12H, (CH₃)₄), 7.68 (m, 2H, 6,7-quinox.), 8.03 (m, 2H, 5,8-quinox.). Anal. calcd for C₁₅H₁₆N₂O: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.96; H, 6.91; N, 11.48.

The third eluted compound, 65, was obtained as an oil and was identified as 2-(quinoxalin-2-yl)-2,4-dimethylpentan-3-one. IR (neat) 3060 w (C-H), 1705 s (C=O), 1550 w, 1490 m, 1465 m, 1095 m, 1025 m, 970 m, 760 s. ¹H NMR (CDCl₃) δ 0.90 (d, 7Hz, 6H, iso-propyl), 1.63 (s, 6H, (CH₃)₂), 2.70 (septet, 7Hz, 1H, iso-propyl), 7.64 (m, 2H, 6,7H-quinox.), 7.93 (m, 2H, 5, 8H-quinox.), 8.68 (s, 1H, 3H-quinox.). Anal. calcd for C₁₅H₁₈N₂O: C, 74.35; H, 7.49; N, 11.56.

GLC analysis indicated a 17.3%, 28.4%, and 30.9% yield of compounds 63, 64, and 65, respectively. The remainder of the reaction was nonvolatile compounds which were apparent unstable, since the crude product turned dark after only a few minutes at room temperature.

Reducing the equivalency of enolate to aromatic chloride to 1:1 gave a 43.4% yield of substitution product 65. No trace of 63 or 64 was detected.

Experiment 29. Dark Reaction of 3-Potassio-3-methyl-2,4-pentandione (66a) with 2-Chloroquinoxaline (60).

Procedure B gives a dark red solution which by GLC analysis on column I (198° C) gave acetamide (70-162 mg), recovered starting material (60, 47%), and a cleaved substitution product (68a) (14.8%). 68a, a yellow compound, was shown to be 2-(quinoxalin-2-yl) butanone (mp, 60-64° C). IR (neat) (solid) 3050 w (C-H), 1685 s (C=O), 1655 s, 1580 s, 1410 s, 1090 s (enol), 760 s. ¹H NMR (CDCl₃) δ 1.64 (d, 7Hz, 3H, α-CH₃), 2.22 (s, 3H, CH₃), 4.20 (quintet, 7Hz, 1H, CH), 7.68 (m, 2H, 6,7H-quinox.), 7.97 (m, 2H, 5,8H-quinox.), 8.72 (s, 1H, 3H-quinox.). Anal. calcd for C₁₂H₁₂N₂O: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.72; H, 6.02; N, 13.74.

Experiment 30. Photostimulated Reaction of 3-Potassio-3-methyl-2,4-pentandione (66a) with 2-Chloroquinoxaline (60).

Procedure A gave by GLC analysis (conditions as in experiment 29) 45% recovery of starting material (60) and 17% yield of cleaved substitution product (68a).

Experiment 31. Inhibited Dark Reaction of 3-Potassio-3-methyl-2,4-pentandione (66a) with 2-Chloroquinoxaline (60).

Procedure B modified by adding 15 mol % (.065 g) of DTBN to the 2-chloroquinoxaline, gave by GLC (conditions same as Experiment 29) a 51% recovery of 2-chloroquinoxaline and < 3% of the cleaved substitution product (68a).

Experiment 32. Dark Reaction of Potassiodiethylmalonate (66b) with 2-Chloroquinoxaline (60).

Procedure B resulted in a colorless solution that crystallized into a 95% recovery of 2-chloroquinoxaline.

Experiment 33. Reaction of Potassium Amide with 1-(Quinoxalin-2-yl)-3,3-dimethylbutan-2-one (61).

Using 17.6 mg of potassium and a small amount of ferric nitrate to generate .45 mmole of KNH_2 in 50 ml of NH_3 , the quinoxaliny ketone (61) was added (.45 mmol, 102.6 mg) in ether (10 ml) to the amide to give a bright orange solution. Stirring for 15 min, quenching, and extraction as described in Procedure A gave a 85% recovery of the starting material (61) and no detectable trace of furoquinoxaline (62).

Experiment 34. Dark Reaction of Pinacolone Enolate and 4-Chloro-2-phenylquinazoline (75a).

Procedure B gave a yellow solid which upon recrystallization from 5 ml of toluene and 2 ml of hexane afforded a 93% yield of 1-(2-phenylquinazolin-4-yl)-3,3-dimethyl-propan-2-one (76a). IR 3080,

3020 (C-H), 3400 (broad, enol), 1680 s (C=O), 1615 s, 1550 m, 1480 m, 1340 m, 1220 m, 1025 m. ^1H NMR (CDCl_3) δ 1.30 (s, 9H, t-Bu), 6.22 (s, 1H, enol), 7.43 (m, 7H, aromatic), 8.17 (m, 2H, aromatic), 15.57 (broad s, 1H, enol). Anal. calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.84; H, 6.68; N, 9.17. Yellow crystals, m p 153-157°C.

Experiment 35. Dark Inhibited Reaction of Pinacolone Enolate and 4-Chloro-2-phenylquinazoline (75a).

Procedure B was repeated, but 20 mol % (.09 g) of DTBN was added to the quinazoline before addition to the enolate. This afforded light yellow crystals that were recrystallized from toluene: hexane to give 97% of 76a, the direct substitution product.

Experiment 36. Dark Reaction of Pinacolone Enolate and 4-Chloro-quinazoline (75b).

4-Chloroquinazoline was synthesized by the method of Armarego in good yield.¹³⁶ Procedure B gives yellow crystals (mp, 118-9°C) after recrystallization from hexane: toluene (4 ml: 1 ml). This was identified as 1-(quinazolin-4-yl)-3,3-dimethylbutan-2-one, 76b. IR (CDCl_3) 3060 w (C-H), 1625 s (C=O), 1602 s, 1580 s, 1560 s, 1490 s, 1395 s, 935 m, 920 m. ^1H NMR (CDCl_3) δ 1.27 (s, 9H, t-Bu), 6.20 (s, 1H, enol), 7.57 (m, 5H, aromatic), 14.7 (broad s, 1H, enol). Anal. calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.78; H, 7.13; N, 12.33.

No trace of starting material could be found, and the substitution product (76b) was isolated in 95% yield.

Experiment 37. Dark Inhibited Reaction of Pinacolone Enolate and 4-Chloroquinazoline (75b).

Procedure B was modified by adding .09 g of DTBN (20 mol %) to the 4-chloroquinazoline before addition to the enolate. This resulted in yellow crystals of 76b isolated by recrystallization as in Experiment 36 in 95% yield. All starting aromatic halide was consumed.

Experiment 38. Dark Reaction of Diisopropylketone Enolate and 2-Chloroquinoline (77).

In a very carefully darkened flask procedure B was carried out. However, quenching of the reaction was performed in the reaction vessel without any appreciable light entering the reaction solution. This resulted in reproducible yields of substitution product, 2-(quinolin-2-yl)-2,4-dimethyl-3-pentanone (79) in 40% yield.⁵⁹ 2-Chloroquinoline was recovered in 55% yield.

Experiment 39. Dark Reaction of Acetone Enolate with 2-Chloroquinoline (77) and 2-Chloropyrazine (54) as Entrainment Agent.

Procedure B was performed with the aromatic halide being a mixture of 2-chloroquinoline and 2-chloropyrazine in 90:10 molar ratio. 1-(Quinolin-2-yl)propan-2-one was formed in 94% yield and the acetylpyrazine was formed in 95% yield based on the equivalents of 2-chloropyrazine used.

Experiment 40. Attempted Dark Reaction of Acetone Enolate with 2-Chloroquinoline (77) and Pyrazine as Entraining Agent.

The same conditions were used as in Experiment 39, but pyrazine was used as entraining agent rather than chloropyrazine. A 17% yield of acetylquinoline was obtained.⁵⁹

Experiment 41. Attempted Dark Reaction of Pinacolone Enolate with 3-Chloro-6-methoxypyridazine (47) and 2-Chloropyrazine as Entrainment Agent.

Using the same conditions as Experiment 39, but the chloropyridazine was used instead of 2-chloroquinoline, gave the same results as Experiment 18. The only exception was the pinacolylpyrazine was obtained in >90% yield based on amount of chloropyrazine used.

Experiment 42. Attempted Dark Reaction of Diisopropylketone Enolate with 2-Chloropyrimidine (21) and 2-Chloropyrazine as Entrainment Agent.

Following the same procedure as in Experiment 39, except 2-chloropyrimidine was used instead of chloroquinoline, gave the same results as experiment 6. The diisopropylketone substituted pyrazine was obtained in >90% yield.

Experiment 43. Attempted Dark Reaction of Acetone Enolate with 2-Bromopyridine and Chloropyrazine as Entrainment Agent.

Using the same procedure as in Experiment 39, except that 2-bromopyridine was used instead of 2-chloroquinoline, no trace of the substituted pyridine was found.³¹ Acetylpyrazine was isolated in >95% yield.

Experiment 44. Photostimulated, Dark and Inhibited Reaction of Pinacolone Enolate with 2,4-Dichloropyrimidine (92).

Procedure A, B, or inhibited (DTBN) procedure A gave the same results. In all cases a light yellow ethereal solution was obtained. PLC silica gel chromatography with ether gave a yellow solid (93) that was recrystallized from toluene, mp 160-61°C. 93 was identified as N-(6-t-butylpyridin-2-yl)cyanamide. IR (neat, solid) 3250 w (N-H), 3090 w (C-H), 2170 s and 2150 s (C≡N, conj.), 1630 s (pyridine), 1605 m (pyridine), 1535 m (N-H bend), 1455 m (t-Bu), 1395 m (pyridine), 1260 m, 1215 m, 1180 m (t-Bu), 990 w, 755 m. ¹H NMR δ 1.43 (s, 9H, t-Bu), 6.63 (d, 7Hz, 1H, 3H pyrid), 7.25 (d, 8.5Hz, 1H, 5H pyrid), 7.71 (quintet, 7Hz and 8.5Hz, 1H, 4-pyridine), 10.0 (broad s, 1H, NH). Anal. calcd for C₁₀H₁₃N₃: C, 68.54; H, 7.48; N, 23.98. Found: C, 68.51; H, 7.70; N, 23.14. This light yellow compound was isolated in 70% yield, mp 154-8° C.

Experiment 45. Photostimulated, Dark, and Inhibited Reactions of Diisopropyl Ketone Enolate and 3,6-Dichloropyridazine (99).

Procedure A, B, or inhibited B all produced the same result. Upon careful evaporation of the ammonia and ether, dilution of the oil with 10 ml of hexane and maintaining the temperature below 30° C resulted in white crystals (decomposition rapid > 50° C). Rinsing the crystals with hexane and vacuum pumping for 8 hr at room temperature gave reddish-brown tar. ¹H NMR of the white crystals gave a reddish solution upon contact with CDCl₃ with shifts as follows: δ 1.20 (m,

12H) and 3.0 (m, 4H). This compound was identified as 2-(3,6-dichloro-4,5-dihydropyridazin-4-yl)-2,4-dimethylpentan-3-one (100). Anal. calcd for $C_{11}H_{16}Cl_2N_2O$: C, 50.20; H, 6.13; N, 10.65. Found: C, 49.51; H, 6.38; N, 10.81.

Allowing this material to stir with silica gel for 24 hr or more resulted in hydrolysis into two compounds 101 and 102 isolated by PLC (60:40, ether:hexane) on silica gel. These compounds were identified as 4-(1,3-dimethyl-2-oxobutyl)-3-chloro-4,5-dihydropyridazin-3-one (101) and 5-(1,3-dimethyl-2-oxobutyl)-3-chloro-4,5-dihydropyridazin-3-one (102). 101 gave IR ($CHCl_3$), 3420 m (N-H), 3250 w (broad, N-H), 1700-1670 s (broad, C=O), 1260 s. 1H NMR ($CDCl_3$) δ 1.05 and 1.07 (d, 7Hz, 6H, isopropyl), 1.12 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 3.22 (septet, 7Hz, 1H, isopropyl), 2.83 (ABC, 2H, CH_2), 3.28 (ABC, 1H, CH), 8.84 (broad s, 1H, N-H). Anal. calcd for $C_{11}H_{17}ClN_2O_2$: C, 53.99; H, 7.00; N, 11.45. Found: C, 54.06, H, 6.61; N, 11.58. mp, 133 $^{\circ}$ C. 102 gave IR identical with 101 and 1H NMR ($CDCl_3$) δ 1.05 (quintet, 7Hz and 2.4 Hz, 6H, iso-propyl), 1.18 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 3.22 (septet, 7Hz, 1H, iso-propyl), 2.31 (AMX, $J_{AX} = 3Hz$ and $J_{AM} = 17.8 Hz$, 1H, CH_2), 2.82 (AMX, 1H, $J_{MX} = 8.8 Hz$, CH_2), 3.51 (AMX, 1H, CH), 9.27 (broad s, 1H, NH), mp 131-3 $^{\circ}$ C.

Both compounds were recrystallized from hexane:toluene, 102 in 48.2% and 101 in 11.4% yields.

Experiment 46. Attempted Dark Reaction of Acetone Enolate with 3,6-Dichloropyridazine (99).

Procedure B gave upon evaporation of the ether a red tar. GLC analysis revealed no major peaks other than starting ketone and some self condensation products of the ketone. TLC on silica gel gave only baseline except with very polar solvents such as alcohols.

Experiment 47. Dark Reaction of Diisopropyl Ketone Enolate and 2,3-Dichloropyrazine (103).

Procedure B was used except double the amounts of K and carbon acid was used. The ether extract by GLC analysis on column V (130° C) gave compound 105 (retention time 3 min, 6.2%), 104 (17 min, 17%), 57 (6 min, 2.3%), and 106 (4 min, 5%). 105 was identified as 3,4-(pyrazin-[b]-yl)-2,2,5,5-tetramethylcyclopentanone. IR (solid) 3060 w (C-H), 1745 s (C=O), 1475 m, 1405 m, 1395 m, 1310 m, 1140 m, 1100 m. ¹H NMR (CDCl₃) δ 1.42 (s, 12H, 2(CH₃)₂), 8.43 (s, 2H, Arom.). Anal. calcd for C₁₁H₁₄N₂O: C, 69.45; H, 7.42; N, 14.72. Found: C, 69.53; H, 7.51; N, 14.90, mp 78° C (white crystals).

106 was the unsymmetrical dimer identical in spectral character to an authentic sample.¹¹⁴

57 was the monosubstitution product with the chlorine reduced off of the aromatic ring. It displayed spectra identical to that found in Experiment 21.

104 was found to be 2-(3-chloropyrazin-2-yl)-2,4-dimethylbutan-3-one. IR (neat) yellow oil, 3050 w (C-H), 1705 s (C=O), 1475 m,

1385 m, 1360 s, 1133 s, 1060 s, 1023 m, 1015 m, 1000 m, 860 m (C-Cl).
 ^1H NMR (CDCl_3) δ 1.13 (d, 7Hz, 6H, iso-propyl), 1.68 (s, 6H, $(\text{CH}_3)_2$),
 2.81 (septet, 7Hz, 1H, iso-propyl), 8.27 and 8.48 (d, 2H, arom.).
 Anal. calcd for $\text{C}_{11}\text{H}_{15}\text{ClN}_2\text{O}$: C, 58.54; H, 6.70; N, 12.41. Found:
 C, 58.30; H, 6.75; N, 12.30.

The remainder of the material was baseline material on TLC and was dark red in color.

Experiment 48. Inhibited Dark Reaction of Diisopropyl Ketone Enolate and 2,3-Dichloropyrazine (103).

Procedure B modified by adding 15 mol % (.074 g) of DTBN to the dichloropyrazine before addition to the enolate, resulted in essentially the same products as described in Experiment 47. Yields were 6.5%, 1.4%, 0%, and 21.5% for compounds 105, 106, 57, and 104, respectively. The remainder of the reaction was tar by TLC.

Experiment 49. Dark Reaction of Pinacolone Enolate and 2,3-Dichloropyrazine (103).

Procedure B yielded a yellow-red oil that by GLC analysis indicated a 71% yield of monosubstitution product 107 (column III at 200°C (retention times 5 min). Spectral evidence for 107 gave the following: IR 3060 w (C-H), 1711 s (C=O), 1623 m, 1480 m, 1385 s, 1087 s, 1065 s, 910 s. ^1H NMR (CDCl_3) δ 1.28 (s, 6H, t-Bu), 2.21 (s, 2H, CH_2), 5.86 (s, .05H, enol), 8.20 and 8.38 (AB, 2Hz, aromatic), 14.0 (broad s, .05H, enol). Anal. calcd for $\text{C}_{10}\text{H}_{13}\text{ClN}_2\text{O}$: C, 56.48; H, 6.16; N, 13.17. Found: C, 56.21; H, 6.23; N, 13.33.

Experiment 50. Inhibited Dark Reaction of Pinacolone Enolate and 2,3-Dichloropyrazine (103).

Procedure B with the modification of adding 15 mol % of DTBN to the 2,3-dichloropyrazine before addition to the enolate resulted in a 70% isolated yield of 107, the monosubstitution product. The yellow oil (107) was obtained from PLC silica gel plate eluted twice with 40:60 methylene chloride:hexane.

Experiment 51. Dark Reaction of Pinacolone Enolate and 2,6-Dichloropyrazine (108).

Procedure B resulted in a yellow solution that gave a 99% isolated yield of 1-(6-chloropyrazin-2-yl)-3,3-dimethylbutan-2-one (109). This compound was prepared by PLC development with 40:60 methylene chloride:hexane) on silica gel. IR (neat) 3040 w (C-H), 1705 s (C=O), 1512 m, 1475 m, 1390 s, 1365 m, 1315 m. ¹H NMR (CDCl₃) δ 1.22 (s, 9H, t-Bu), 4.02 (s, 2H, CH₂), 8.32 (s, 1H, pyra.), 8.37 (s, 1H, pyra.). Anal. calcd for C₁₀H₁₃ClN₂O: C, 56.48; H, 6.16; N, 13.17. Found: C, 56.33; H, 6.31; N, 13.32.

Experiment 52. Inhibited Dark Reaction of Pinacolone Enolate and 2,6-Dichloropyrazine (108).

Procedure B modified by addition of 15 mol % of DTBN to the dihalopyrazine before addition to the enolate resulted in a 90% isolated yield of 109 (the monosubstitution product) by the methods described in Experiment 51.

Experiment 53. Photostimulated Reaction of Pinacolone Enolate and 3,5-Dichloropyridine (82).

Following procedure A except doubling the amount of potassium and carbon acid resulted in a 80% yield of disubstitution product 83. This yield was determined by GLC on column IV at 205° C (retention time of 12 min). IR (CHCl₃) 1701 s (C=O), 1470 s, 1460 s, 1210 s, 1050 s. ¹H NMR (CDCl₃) δ 1.20 (s, 18H, t-Bu), 3.77 (s, 4H, CH₂), 7.42 (m, 1H, 4H Py.), 8.3 (m, 2H, 2,6H Py.). Anal. calcd for C₁₇H₂₅NO₂: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.02; H, 8.92; N, 5.10: mp 103-5° C, faint yellow needles (heptane:benzene).

Experiment 54. Inhibited Photostimulated Reaction of Pinacolone Enolate and 3,5-Dichloropyridine (82).

Procedure A with 10 mol % of DTBN (.043 g) added to the dichloropyridine before addition to the enolate, resulted in a light yellow oil that by GLC conditions previously described (Experiment 53) gave a 50% recovery of starting material and 15.4% yield of disubstitution product 83.

Experiment 55. Dark Reaction of Pinacolone Enolate and 3,5-Dichloropyridine (82).

Procedure B gave by GLC analysis (see Experiment 53) 60-70% recovery of starting dichloropyridine (82) and 20% yield of disubstitution product 83.

Experiment 56. Photostimulated Reaction of Pinacolone Enolate and 2,3-Dichloropyridine (84).

The same conditions described in Experiment 53 resulted in a 76.4% yield of disubstitution product 85 by GLC analysis (column IV, 165° C, retention time 30 min). IR 1705 s (C=O), 1480 m, 1220 vs, 1060 m. ¹H NMR (CDCl₃) δ 1.24 and 1.28 (s, 18H, t-Bu), 3.84 (s, 2H, 3-position CH₂), 4.05 (s, 1.6H, 2-position CH₂), 5.24 (s, .2H, enol), 6.88, 7.12, and 7.37 (m, 2H, 4,5-position py.), 8.07 and 8.46 (d, .2H and .6H respectively, 6-position py.), 16.0 (broad s, .2H, enol). Anal. calcd for C₁₇H₂₅NO₂: C, 74.14; H, 9.15; N, 5.09. Found: C, 72.51; H, 8.63; N, 4.92.

85 was isolated as a yellow oil (63% yield) from PLC silica gel developed with 30:70 ether:hexane.

Experiment 57. Dark Reaction of Pinacolone Enolate and 2,3-Dichloropyridine (84).

Procedure B gave a 70-80% recovery of the dichloropyridine by GLC analysis as previously described in Experiment 56.

Experiment 58. Photostimulated Reaction of Pinacolone Enolate and 2,5-Dibromopyridine (86).

Following the same procedure described in Experiment 53, resulted in a 54% isolated yield of the disubstitution product (87). GLC analysis indicated 85-90% of 87. IR 1701 s (C=O), 1470 m, 1205 m, 1050 m, 890 m. ¹H NMR (CDCl₃) δ .97 (s, 1H, t-Bu), 1.08, 1H, t-Bu), 1.27 (s, 16H, t-Bu), 3.80 (s, .15H, CH₂ (3-position)), 3.83 (s, 1.85H,

CH₂ (3-position)), 4.04 (s, 1.85H, CH₂ (2-position)), 5.46 (s, .15H, enol (2-position)), 6.97 and 7.27 (d, 8Hz, .15 and .85 H (respectively), 3H py.), 7.52 and 7.58 (quintet, 8Hz (J_{3,4}) and 2Hz (J_{4,6}), .15H and .85H (respectively), 6H py.), 8.14 and 8.43 (d, 2Hz, .15 and .85H (respectively), 6H py.), 14.0 (broad s, .15H, enol). Anal. calcd for C₁₇H₂₅NO₂: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.19; H, 9.31; N, 5.09. mp 87.5-88.5°C, yellow needles from heptane.

Experiment 59. Dark Reaction of Pinacolone Enolate and 2,5-Dibromopyridine (86).

Procedure B resulted in a 60% recovery of starting material (86) by GLC analysis as described in Experiment 58. Less than 3% of the disubstitution product 87 was noted.

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THE $S_{RN}1$ REACTIVITY OF SELECTED
AROMATIC DIAZINES

by

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(ABSTRACT)

The scope and limitations of aromatic diazines undergoing nucleophilic substitution reactions occurring via a radical-chain ($S_{RN}1$) mechanism were investigated. The study was conducted on a series of mono- and dihalogenated aromatic diazines interacting with various ketone enolates in ammonia. Results indicate that this previously unrecognized reaction pathway in these nitrogen heterocycles is easily obtained and should prove of great synthetic utility in preparation of substituted diazines.

Aromatics that were probed include 2-chloropyrimidine, 4-chloro-2,6-dimethoxypyrimidine, 3-chloro-6-methoxypyridazine, 2-chloropyrazine, 2-chloroquinoline, 2-chloroquinoxaline, 4-chloro-2-phenylquinazoline, 4-chloroquinazoline. The nucleophiles used to test for the radical character ($S_{RN}1$) of the aromatics include acetone, diisopropyl ketone, and pinacolone enolates. Reaction of these nucleophiles with the various haloaromatics resulted in substitution at the carbon bearing the nucleofuge or an addition to the aromatic at a site other than that bearing the leaving group.

2-Chloropyrimidine underwent substitution under photostimulated conditions, but addition processes ($S_NANRORC$) were in competition with

the $S_{RN}1$ mechanism in this case. 4-Chloro-2,6-dimethoxy pyrimidine underwent smooth substitution under photostimulation, but addition processes were not a major side reaction. 3-Chloro-6-methoxy pyridazine reacted slowly in the dark to give substitution products via a $S_{RN}1$ pathway; however, addition products were also formed. Irradiation stimulated the substitution process in this case. 2-Chloropyrazine underwent smooth $S_{RN}1$ reaction in the dark with ketone enolates. 2-Chloroquinoline reacted slowly with diisopropylketone in the dark via a radical-chain process. 2-Chloroquinoxaline gave a very fast substitution process that was entirely radical-chain in character. In addition, products were formed from nucleophilic attack at the 3-position. Both 4-Chloro-2-phenylquinazoline and 4-chloroquinazoline gave good substitution via a non-radical process.

Dihaloaromatics that were studied are 3,5-dichloropyridine, 2,3-dichloropyridine, 2,5-dibromopyridine, 2,3-dichloropyrazine, 2,6-dichloropyrazine, 3,6-dichloropyridazine, and 2,4-dichloropyrimidine. The isomeric dihalopyridines in all cases gave disubstitution products via the $S_{RN}1$ process. 2,3-Dichloropyrazine and 2,6-dichloropyrazine showed very little evidence of radical character in their substitution reactions. Monosubstitution products were isolated in both cases in high yield. 3,6-Dichloropyridazine gave addition products with no trace of substitution compounds or radical activity. 2,4-Dichloropyrimidine gave no substitution products but underwent an $S_{N}ANRORC$ reaction to give pyridinylcyanamides.

The viability of the $S_{RN}1$ reaction as well as the requirement for photostimulation was shown to correlate very well with the one electron reduction potential of the parent aromatic substrate. The reactions of the dihaloaromatics indicated that the activating influence of the additional halogen was larger for ionic processes than that of electron transfer reactions. Also, in cases in which the dihaloaromatics proceeded to substitute via the $S_{RN}1$ mechanism, formation of mono-substitution or a predominance of disubstitution product was indicated to be related to the spin density of the unpaired electron on the carbon bound to the nucleofuge in the intermediate radical anion. Results from the dihalopyridine reaction point to the fact that the $E_{1/2}$ value of the parent heteroaromatic, as well as the spin density mentioned previously, plays a role in the lifetime of the intermediate radical anions of haloheteroaromatics.