THE EFFECTS OF SOLVENTS AND NUCLEOPHILES ON HETEROAROMATIC $S_{RN}1$ REACTIONS

by

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CHAPTER I

Synopsis: The discovery of, proposed mechanism for, previous work related to, and goals of the present work in regard to the $S_{RN}1$ mechanism are outlined.

During their study of the reactions of 5- and 6-halopseudocumenes with KNH_2 in liquid ammonia, Kim and Bunnett observed an anomaly in the proportion of products obtained when the halogen was iodine rather than bromine or chlorine.[1] They concluded that the unusually large percentage of direct amination observed with aromatic iodides resulted from a radical mechanism similar to that proposed a few years earlier by Kornblum[2] and Russel[3] for certain benzylic halides.

The mechanism proposed for this "new" type of aromatic nucleophilic substitution is given in equations 1 through 5 in Scheme I. Ar-X

SCHEME I

$$Ar\text{-}X + N^- \rightarrow [Ar\text{-}X]^{\cdot -} + N^{\cdot} \quad (1)$$

$$[Ar\text{-}X]^{\cdot -} \rightarrow Ar^{\cdot} + X^- \quad (2)$$

$$Ar^{\cdot} + N^- \rightarrow [Ar\text{-}N]^{\cdot -} \quad (3)$$

$$[Ar\text{-}N]^{\cdot -} + Ar\text{-}X \rightarrow Ar\text{-}N + [Ar\text{-}X]^{\cdot -} \quad (4)$$

$$Ar^{\cdot} + R\text{-}H \rightarrow Ar\text{-}H + R^{\cdot} \quad (5)$$

represents some aromatic system with nucleofugic[4] group X and N^- represents a suitable nucleophile. Chain initiation is depicted in equation 1 and is postulated to involve an electron transfer from the nucleophile to Ar-X generating its radical anion. In the three ensuing propagating steps, this radical anion expels the nucleofuge, as shown in equation 2, leaving the aromatic radical available for attack by the nucleophile (equation 3) and thus producing the product radical anion which may

transfer an electron, as in equation 4, to unreacted Ar-X. One of the possible chain terminating steps is given in equation 5. It shows the aromatic radical abstracting a hydrogen atom from a suitable donor represented as R-H. Other termination steps, such as combination of aryl radicals or reduction of these radicals to aryl anions followed by protonation are conceivable.

The similarity of this overall mechanism to the S_N1 mechanism for aliphatic nucleophilic substitution shown in Scheme II is apparent.

SCHEME II

$$RX \rightarrow R^+ + X^- \quad (6)$$

$$R^+ + N^- \rightarrow RN \quad (7)$$

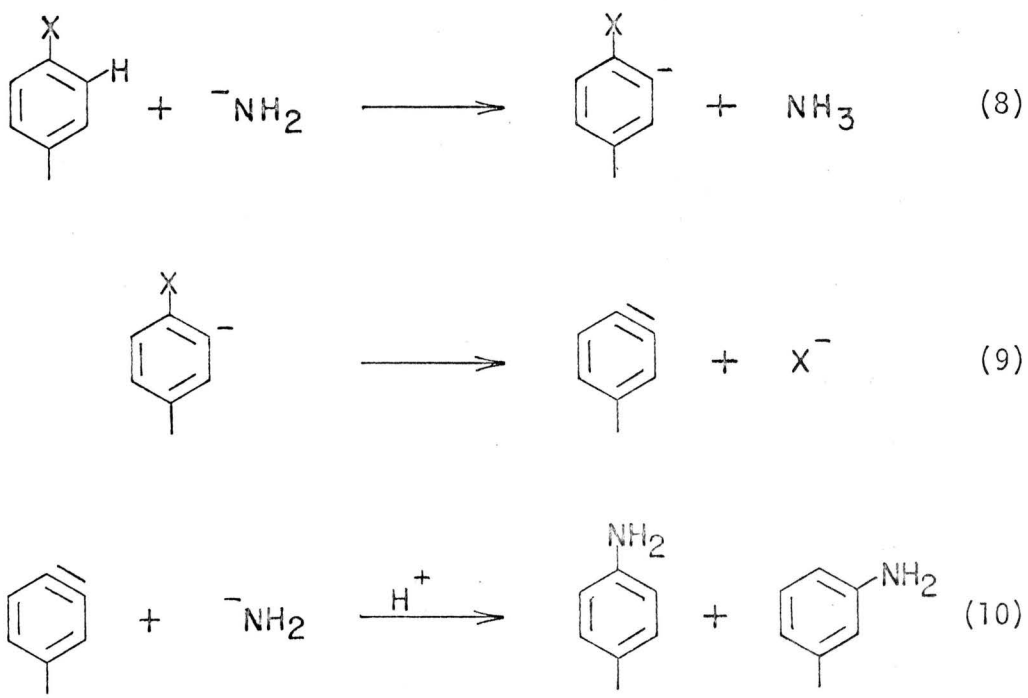
Equations 2 and 3 of Scheme I are identical to equations 6 and 7 except that the former involve substrate systems which are one electron richer than those of Scheme II. This similarity prompted Bunnett to coin the acronym $S_{RN}1$ for the newly discovered mechanism. $S_{RN}1$ signifies that the reaction is a substitution process that involves radical intermediates, attack by a nucleophile, and the unimolecular bond fission (equation 2) of a radical anion.

The novelty of the $S_{RN}1$ mechanism lies in its use in nucleophilic aromatic substitution of unactivated aromatic halides. Aromatic halides were generally thought to be unreactive toward nucleophiles unless there were electron-withdrawing (activating) groups attached to the aromatic ring.[5] Nucleophilic substitutions have been realized with unactivated aromatic halides. However, these substrates are frequently subjected to harsh reaction conditions in order to force substitution to occur.

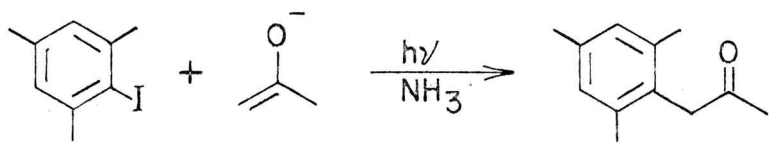
The extreme differences between the conditions required for and the products obtained from the reactions of various aromatic halides with nucleophilic reagents leads one to suspect that more than one mechanistic pathway is operating. Actually, there are several mechanisms proposed for aromatic nucleophilic substitution[6,7] of which three are illustrated below. The reader who is interested in some of the other known methods and mechanisms of aromatic nucleophilic substitutions, which are not directly related to this research, is referred to Zoltewicz's discussion[6] on metal ion catalysts and arenediazonium ions (S_N1), Semmelhack's review[8] on arene-metal complexes in organic synthesis, and Chupakhim's and Postovskii's review on S_NH reactions.[9]

The benzyne mechanism[10] shown in Scheme III requires that a hydrogen

SCHEME III



ortho to the halogen be present in order to produce the reactive aryne intermediate (equation 9). Its heterocyclic analogue, the hetaryne mechanism, has been discussed by Kauffman and Wirthwein.[11] This mechanism cannot explain the substitution of the halogen in iodomesitylene shown in equation 11.[12] There are no ortho hydrogens to be removed,

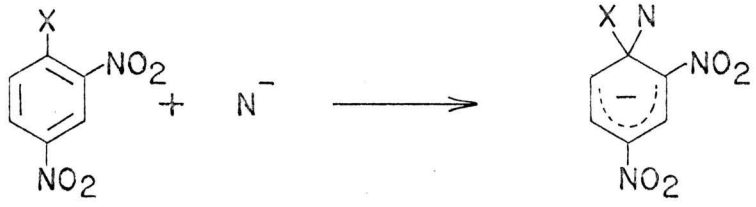


82 % (11)

thus some other mechanism must be operating. The insensitivity to steric barriers in this example is interesting.

The S_NAr2 mechanism[7,13] shown in Scheme IV could be an alternative

SCHEME IV



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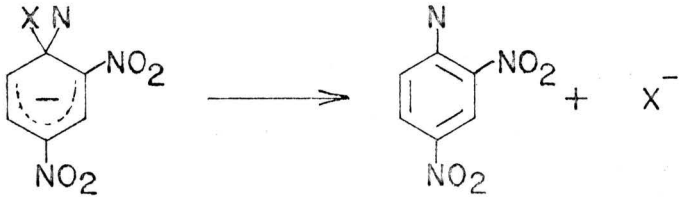


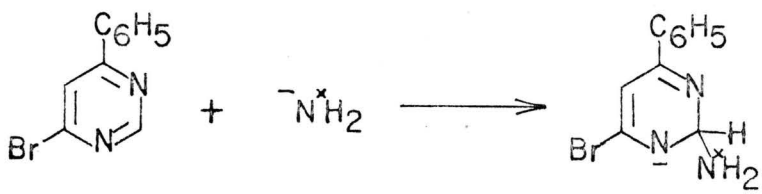
(13)

mechanism for the example above. However, researchers have found that the relative order of halogen displacement in S_NAr2 substitution is $F \gg Cl \simeq Br \geq I$.[13] The reverse order of halogen reactivity has been found with $S_{RN}1$ reactions.[14,15] An additional problem with the S_NAr2 mechanism is its inability to explain the reactivity of aromatic systems

lacking electron withdrawing (activating) groups.

Whereas both the benzyne and S_NAr2 mechanisms are applicable to both carboaromatic and heteroaromatic systems, the S_N(ANRORC) or ring cleavage mechanism,[16] shown in Scheme V, is peculiar to only nitrogen-

SCHEME V



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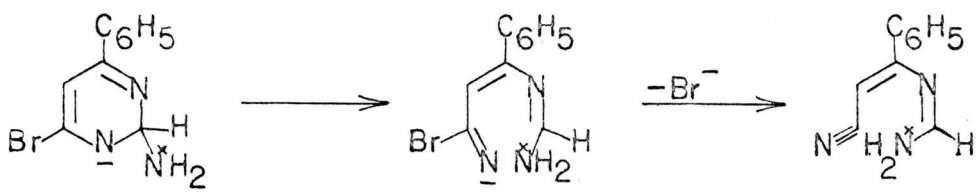

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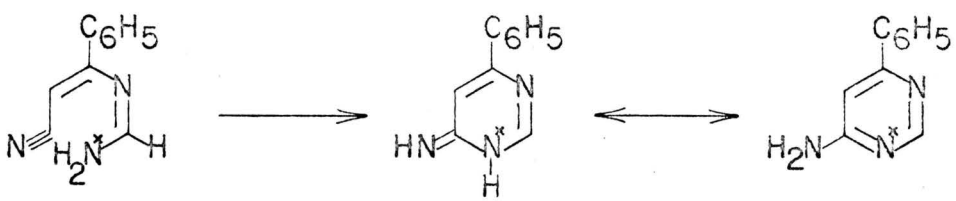
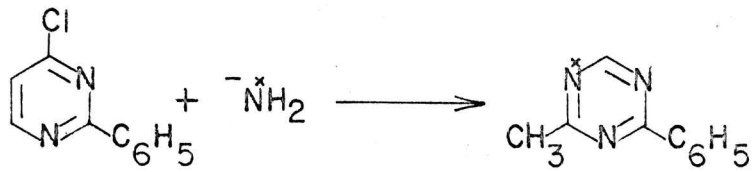


(16)

containing heteroaromatic halides. The acronym, S_N(ANRORC), represents a nucleophilic substitution in which the initial addition of the nucleophile causes ring opening and subsequent ring closure occurs such that one of the original ring atoms is exchanged. The major feature of this mechanism is that nucleophilic attack occurs at a position other than that occupied by the nucleofuge. This is in contrast to all of the above mechanisms in which the nucleophile attacks at the nucleofuge-bearing carbon. Ring transformations are also possible by this mechanism.

Equation 17 shows a transformation that 4-chloro-2-phenyl-pyrimidine



(17)

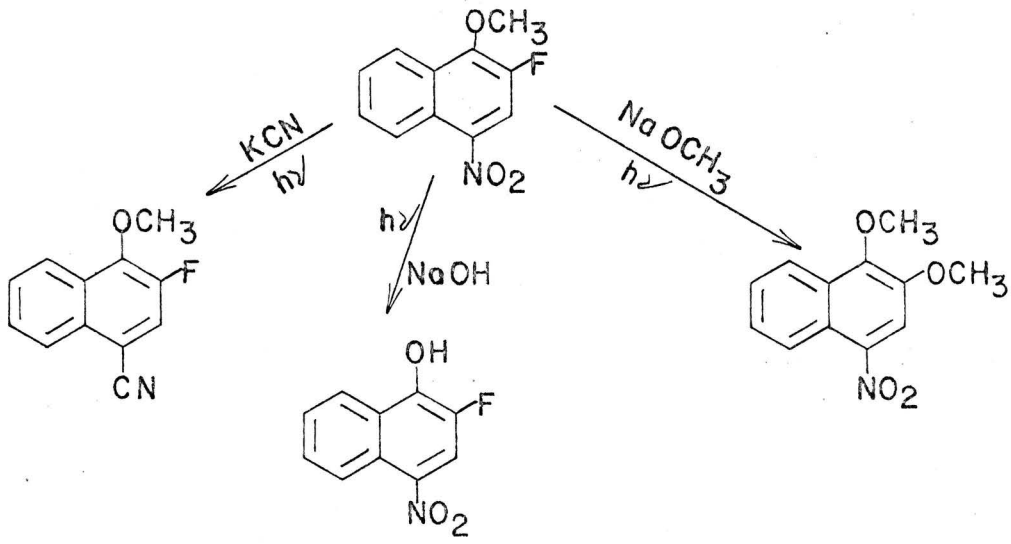
undergoes upon treatment with KNH_2. Thus, the absence of ring-transformed products in $S_{RN}1$ reactions is a clue that the S_N(ANRORC) mechanism is not in operation.

Both the S_N(ANRORC) and S_NAr2 mechanisms are ionic processes and, therefore, should not be hampered by the presence of radical scavengers as $S_{RN}1$ reactions are known to be. The radical scavengers commonly used for inhibition studies are p-dinitrobenzene (pDNB), di-t-butyl nitroxide (DTBN), oxygen, benzophenone, and ferric chloride.[18,19] These substances are easily reduced and interfere with electron transfer by becoming the preferred election acceptor system.[20]

In addition to the foregoing three mechanisms there is another substitution process which should be mentioned. Photosubstitution of activated aromatic substrates bearing appropriate nucleofuges and involving their π triplet states are known to occur.[21,22] These substitutions are not chain reactions and the orientation rules for these photosubstitutions are usually contrary to those observed for ground state substitutions. Scheme VI is an illustrative example and suggests why there has not been an all-encompassing mechanism proposed for these excited state reactions.

The key to $S_{RN}1$ reactions seems to be the establishment of conditions conducive to electron transfer. $S_{RN}1$ reactions are known to be

SCHEME VI



stimulated by dissolved potassium metal in liquid NH_3, by near ultraviolet light,[23] by heat,[18] and by electrochemical means.[24,25] However, there is little proof as to the exact nature of the initiation process. Electron transfer to the substrate was believed to be initiated by the nucleophile,[26] but activation of the nucleophile for this transfer would seem to be required. Stimulation may be indirect as would seem likely for the photoreactions, though in reactions stimulated by free electrons, a direct electron transfer to the aromatic substrate seems more reasonable. Support for the presence of radicals and also the unimolecular nature of $S_{RN}1$ reactions has been obtained from kinetic studies using ESR.[27]

Most of the synthetic work with carboaromatic systems has involved benzenes with I, Br, Cl, F, SC_6H_5, NMe_3^+, and $OPO(OEt)_2$ as nucleofuges.[28] Halonaphthalenes[29] and halophenanthrenes and haloanthracenes[12] have also been observed to participate in $S_{RN}1$ reactions. With these

systems, numerous nucleophiles have been tried including ketone enolates, dianions of β-diketones, thiophenoxide, amide, ester enolates, α-cyanoalkyl anions, picolyl anions, diethyl phosphite anion, and alkyl sulfides.[28] Liquid ammonia has been the predominant solvent for these reactions because of its low reactivity with radicals, its low acidity, its capacity to be easily dried and its low cost. Dimethyl sulfoxide, dimethylformamide, acetonitrile, and N,N-dimethylacetamide have been used with some success as solvents for these reactions.[30]

The $S_{RN}1$ reactions of heterocyclic aromatic halides have not been extensively explored. Prior to 1974, the only observations of heteroaromatic $S_{RN}1$ type reactions were those of Zoltewicz's 4-bromoisoquinoline with sodium thiophenoxide,[31] van der Plas' halopyrimidine with potassium amide,[32] and Wolfe's 2-chloroquinoline with dilithiobenzoylacetone.[33] The latter observation initiated this research group's entry into the study of $S_{RN}1$ reactions of nitrogen containing heteroaromatic halides. Further research showed that lithioacetone would react with 2-chloroquinoline under photostimulation in liquid ammonia.[34] Later, it was observed that a variety of potassio ketones could be 2-quinolylated by a similar process.[35] The isomeric bromopyridines,[15] the 2-halopyrimidines,[36] and 2-chloropyrazine[36] have been shown to possess $S_{RN}1$ reactivity toward ketone enolate nucleophiles. Generally speaking, the heteroaromatics tend to show more $S_{RN}1$ reactivity than their carboaromatic analogues,[15,28] as is indicated by the shorter reaction times required to effect substitution.

Using the above mentioned background information as a springboard,

this dissertation hopes to explore the synthetic utility of heteroaromatic $S_{RN}1$ reactions by determining the feasibility of these reactions in solvents other than liquid ammonia and by observing the reactivity of these halides with some non-ketone nucleophiles. Lastly, a brief study done jointly with Mr. M. C. Sleevi and dealing with reductive dehalogenations which can accompany $S_{RN}1$ reactions is given.

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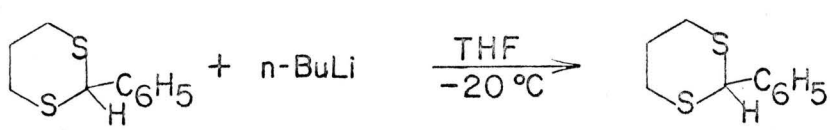
CHAPTER II

Synopsis: The effectiveness of some solvents, including THF, DME, DMF, and DMSO, as media for heteroaromatic $S_{RN}1$ reactions is presented.

Most of the initial investigations concerning the $S_{RN}1$ mechanism were focused on the types of nucleophiles and substrates that could be combined.[1,2] Liquid ammonia was the solvent usually used in these studies. Many other solvents have been employed as media in syntheses involving anions.[3] Thus, their use as solvents $S_{RN}1$ reactions would make this reaction type more synthetically accessible and flexible.

Assuming that these reactions will occur in other solvents, the testing of other nucleophiles that may not be conveniently generated in liquid ammonia may be done. One could also explore the generation of anions with a wide variety of bases not commonly used in liquid ammonia. As an example, the formation of the lithium anion of 2-phenyl-1,3-dithiane in THF is shown in equation 1.[4]



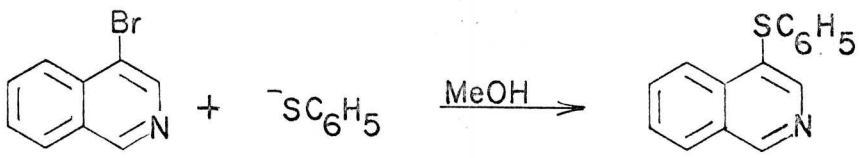
(1)

In choosing a reaction solvent for these reactions, one must be aware of certain limitations. For general applicability and convenience, the chosen solvent should be readily available, easily purified, and relatively inexpensive, since large volumes of it, relative to the reactants, are used. Carbanion reactions usually require anhydrous conditions, thus the facile elimination of water from the solvent is desirable. In addition, solvents for anion reactions should not be so

acidic as to quench the anions formed. The solvent's inertness to radicals and radical anions is required since $S_{RN}1$ reactions involve these intermediates. For reactions that are to be photostimulated, a solvent that absorbs strongly in the near ultraviolet-visible region (300-750 nm) may prevent initiation of these reactions. Lastly, a solvent that can be easily removed from the products is preferred, especially for synthetic applications.

The solvents that immediately appear to meet these requirements are certain ethereal and dipolar aprotic solvents. Bunnett and coworkers have tried some of these solvents as media for their $S_{RN}1$ reactions of selected carboaromatic halides.[5] They obtained satisfactory results using potassium t-butoxide (t-BuOK) as the base for generating various nucleophilic anions in acetonitrile, t-butyl alcohol, dimethyl sulfoxide (DMSO), N,N-dimethylformamide (DMF), 1,2-dimethoxyethane (DME) and N,N-dimethylacetamide (DMAC). Their results from reactions in tetramethylenesulfone, N-methyl-2-pyrrolidone and hexamethylphosphoramide (HMPA) were less successful. The yields of substitution products were generally lower than those of the corresponding reactions in liquid ammonia. Recently, Rajan reported that reactions of phenyl halides with phenoxide ion in aqueous t-butyl alcohol occur via the $S_{RN}1$ mechanism when catalyzed by sodium amalgam;[6] however, this anion is unreactive in liquid ammonia.[7]

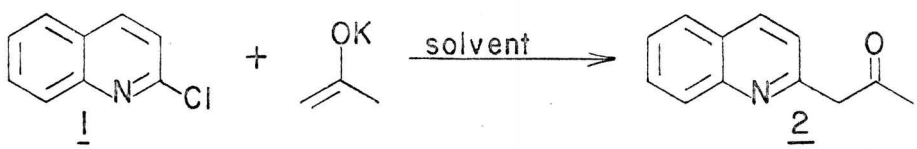
The first observation of heteroaromatic $S_{RN}1$ reactions in a solvent other than liquid ammonia was made by Zoltewicz and Oestreich for the reaction shown in equation 2.[8] Yamaguchi and van der Plas observed the



(2)

$S_{RN}1$ reactions of potassium superoxide with 2-chloroquinoline and 1-bromoisoquinoline without photostimulation in DMSO. No reaction of 3-bromoquinoline with this nucleophile was observed in DMSO unless 18-crown-6 was present.[9] Outside of these studies, all other work with heteroaromatics was done using liquid ammonia as a solvent.[10,11,12,13,14,15] The present work is the first to look at solvent effects on heteroaromatic $S_{RN}1$ reactions.

The model reaction system for testing these solvents is shown in equation 3. It was selected because of its simplicity and because of



1 2 (3)

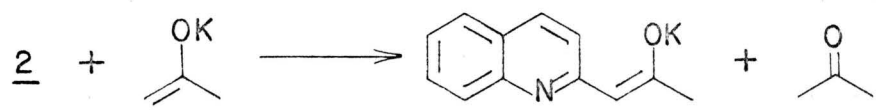
the facility with which it proceeds by the photostimulated $S_{RN}1$ mechanism in liquid ammonia.[13] This well characterized system was ideal for making comparisons with the solvents that were to be tested. When this study was begun 2-chloroquinoline (1) was the most reactive halogenated heterocycle known to participate in these reactions. However, current research has shown that some other halogenated azines are more reactive.[16] The potassium salt of acetone was chosen as the nucleophile because potassium enolates had been shown to be more reactive than the other alkali metal salts in liquid ammonia.[13]

The solvents initially chosen for this study were THF, DME, DMF,

and DMSO. These solvents have been frequently used in various anion reactions[3] and it would be useful to ascertain their suitability as solvents for heteroaromatic $S_{RN}1$ reactions.

To alleviate the problems associated with generating potassioacetone from potassium amide in these solvents, the procedure of Brown[17] was followed. He reported that potassium hydride was an effective base for generating the potassium salts of numerous ketones in ethereal solvents. Since the procedure for working with this reagent was quite adaptable for use in DMF and DMSO as well, his method for anion formation was used.

The ratio of potassioacetone to 2-chloroquinoline (1) chosen for this study was 3.75:1. In addition to maintaining the closest parallel to the corresponding reaction in liquid ammonia, this stoichiometry was selected to circumvent a problem inherent in this system. The methylene hydrogens of 2, which are activated by adjacent aromatic and carbonyl groups, are more acidic than the α-hydrogens of acetone. Thus, as shown in equation 4, there is a loss of one additional molecule of acetone



(4)

enolate for the ionization of each molecule of product.

Finally, two levels of irradiation were employed for these reactions. The lower intensity irradiations, with an approximate wavelength range of 350-750 nm,[18] were performed in a "Butina Reactor" (see Experimental Section). The higher intensity irradiations, with a wavelength

range of 300-350 nm, were performed in a Rayonet RPR-204 photochemical reactor.[19] All of these variables were incorporated into this study and the results are described below.

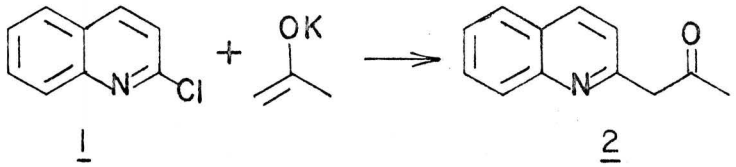
Discussion and Results

The reaction of the model system (equation 3) in THF, DMF, and DME afforded the results shown in Table I. Each entry represents the average of at least two experiments and the percentages were determined by gas chromatographic (GC) analysis using the internal standard method.[20]

Upon general examination of these data, certain trends were noticed. The first seven experiments (group I), which are photostimulated reactions, show good percentage conversion of 1 to product 2 in all three solvents. The dark reactions of experiments 8, 9, and 10 (group II) in the same solvents also show some reaction of 1, but not as much as was observed upon irradiation (group I). Essentially, unreacted 1 is the predominant component in the photostimulated reactions of experiments 11-18 (group III) carried out in the presence of inhibitor. The last six (19-24) experiments (group IV), all of which are inhibited dark reactions, show almost no conversion to product 2.

That the reactions of potassioacetone with 1 proceed by the $S_{RN}1$ mechanisms in the three solvents listed in Table I is supported by the results of the inhibition experiments. The percentage of 2 formed in the reactions of group III, in which only five mole percent (based on 2) of the radical scavengers, pDNB and DTBN, were used, was decreased from that formed in the reactions of group I. A similar, but less marked, comparison can be made of groups II and IV. These reactions are stimulated photochemically as is apparent from the increased yields of group

TABLE I



1 2

Expt. No.	Solvent	Time(h)	Conditions[a]	% Composition[b] 1	2
1	THF	1.0	I	13	82
2	THF	0.25	I	38	52
3	THF	1.0	i	28	53
4	DMF	1.0	i	3	74
5	DMF	0.5	i	33	54
6	DMF	0.25	i	27	52
7	DME	1.0	i	59	28
8	THF	1.0	Dk	61	28
9	DMF	0.25	Dk	44	36
10	DME	1.0	Dk	78	9
11	THF	1.0	I,DTBN	75	17
12	THF	1.0	I,pDNB	78	14
13	THF	1.0	i,DTBN	90	8
14	THF	1.0	i,pDNB	88	3
15	DMF	0.25	i,DTBN	62	13
16	DMF	0.25	i,pDNB	61	15
17	DME	1.00	i,DTBN	90	<2
18	DME	1.00	i,pDNB	85	<2
19	THF	1.00	Dk,DTBN	86	<2
20	THF	1.00	Dk,pDNB	77	<2
21	DMF	0.25	Dk,DTBN	74	8
22	DMF	0.25	Dk,pDNB	92	4
23	DME	1.0	Dk,DTBN	87	2
24	DME	1.0	Dk,pDNB	84	<2

[a] I (high intensity) and i (low intensity) represent irradiations of 300-350 nm and 350-750 nm, respectively. Dk represents a dark reaction. DTBN (di-t-butyl nitroxide) and pDNB (p-dinitrobenzene) are radical inhibitors.

[b] The percentages were determined by gas chromatographic analysis using the internal standard method.[20]

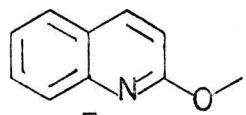
I relative to that of group II. However, unlike the dark reaction of the model system in liquid ammonia, there is some reaction occurring in the dark in these solvents.[13]

Focusing first on the results obtained in THF, it was observed from experiments 1 and 2 that longer reaction time increased the yield of 2-acetonylquinoline (2). There is a significant (28%) dark reaction in this solvent (experiment 8), but the yield is increased when the reactants are irradiated (experiment 3) at low intensity. High intensity irradiation (experiment 1) increased the yield even more, almost as high as was observed (90%) for the reaction of potassioacetone with 1 in liquid ammonia. Inhibition, with pDNB or DTBN, of the dark and low intensity photostimulated reactions (experiments 19, 20 and 13, 14 respectively) is effective. However, inhibition of the high intensity photosubstitutions (experiments 11 and 12) were not as good, presumably because of consumption of the inhibitor through many more attempted chain initiations.

Dimethoxyethane (DME) is another commonly used ether solvent. The data obtained from $S_{RN}1$ reactions in this solvent show that there is a photostimulated process occurring even though the rate is slow (experiments 7 and 10). Experiments 17, 18, 23, and 24 show that the reactions in this solvent are inhibited by radical scavengers and are, therefore, proceeding via the $S_{RN}1$ mechanism.

Smid[21] reported that DME is just as good as, or better than, THF as a medium for radical reactions. However, he also found that alkoxide impurities had an effect on radical reactions. It is very likely that

alkoxide impurities were present in the DME used for the present reactions because 3 and 4 (less than 5%) were found as side products in



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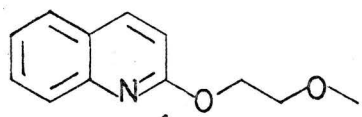


4

these reactions. These two compounds arise from a substitution of the chlorine in 1 by methoxide and methoxyethoxide anions. Surprisingly, Zoltewicz found that excess methoxide ion stimulated the $S_{RN}1$ reaction shown in equation 2.[8]

Of these three solvents, the $S_{RN}1$ reactions of potassioacetone with 1 in DMF were the fastest (experiments 4, 5, and 6). In order to obtain yields comparable to those in liquid ammonia, less light energy was required for photostimulation. There was a sizable dark reaction in this solvent (experiment 9). However, as observed in the inhibited experiments 15, 16, 21, and 22, both dark and irradiated reactions in DMF did involve radical intermediates. The general material balances of the reactions in this solvent were fairly consistent among themselves but were poorer than those obtained using other solvents. This difference may have been due to the method of preparing the samples for analysis (see Experimental Section).

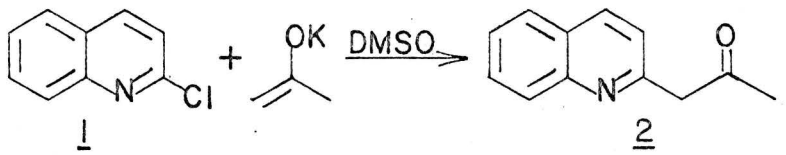
Initially, only pDNB was used to inhibit these reactions. However, because of the intense coloring of the reaction mixtures upon photostimulation, especially with DMF as the solvent, some doubt arose as to whether its inhibitory action was due to radical anion trapping or due to the prevention of photostimulation by light adsorption. DTBN mixed

with the reactants does not produce an intensely colored solution. Upon comparing the effects of the two inhibitors (experiments 15 and 16), there was found to be no significant difference between their effectiveness. Thus pDNB's inhibitory action, in this system, was due to radical anion trapping[22] and not light adsorption.

In addition to reactions in the above solvents, a series was attempted using DMSO as the reaction medium. Data for representative experiments are given in Table II. The first things to observe about this table are experiments 1 and 2. These were conducted under essentially identical conditions and should have given similar results. The data obtained from the remaining experiments in this solvent were just as inconsistent. Unlike the results obtained in the other solvents, it appears as though the best yields are obtained in the absence of photostimulation.

Scamehorn and Bunnett[23] have reported successful results in this solvent for the reactions of halobenzenes with the potassium enolate of pinacolone. They used t-BuOK as the anion generating base. It was felt that by using this base, perhaps more consistent data could be obtained. However, again gross inconsistencies were observed for this system as indicated by the poor material balances (experiments 3, 6, and 10). The most interesting observation from these data is the relative times required to obtain a reasonable amount of substitution using the different anion-generating bases. Reactions using KH as the initial base are essentially complete after 15 minutes, whereas a comparable amount of reaction using t-BuOK as the initial base requires more than

TABLE II



1 2

Expt. No.	Time(min)	Conditions[a]	Base[b]	% Composition[c] 1	2
1	5	i	KH	24	37
2	5	i	KH	62	49
3	5	i	t-BuOK	83	8
4	15	i	KH	..	32[d]
5	15	i	t-BuOK	60	18
6	60	i	t-BuOK	15	37
7	5	i,DTBN	KH	45	11
8	5	i,DTBN	t-BuOK	94	..
9	5	Dark	KH	..	69
10	60	Dark	t-BuOK	30	40

[a] i represents irradiation between 350-750 nm. DTBN is di-t-butyl-nitroxide, a radical scavenger.

[b] KH represents potassium hydride and t-BuOK represents potassium t-butoxide.

[c] Percentages were determined by GC analyses using the internal standard method.[20]

[d] Value represents an isolated yield.

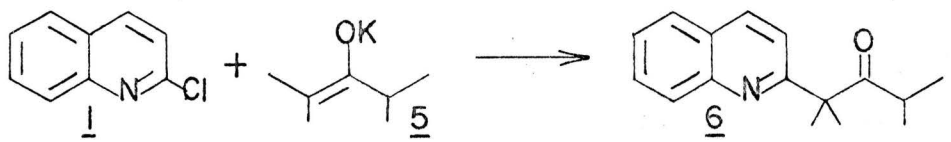
an hour. Clearly, some effect due to the base is present.

The testing of $S_{RN}1$ reactions in diethyl ether and benzene proved to be ineffectual. After two hours of irradiation between 300-350 nm, only 9% of 2 was produced and 89% of 1 remained when diethyl ether was the solvent. Similarly, after one hour of irradiation (350-750 nm) in benzene 89% of 1 remained unreacted.

From the previously mentioned observations, certain generalizations about the relative effectiveness of the solvents could be made. Each of the four solvents, after purification, was easier to handle than liquid ammonia. The solvent most readily purified was THF because it is low boiling and thus, there was no need to perform vacuum distillations of the solvent as was necessary, particularly, with DMSO which decomposes at reflux.[24] The problems associated with the fractionation of alcohol and ether contaminants in DME were not present with THF. Both THF and DME were easily removed from the reaction mixtures, whereas residual DMF and DMSO, which interfered with analyses, continued to linger. In the reactions conducted in DME and DMF, there were more side products (about 5%) observed, many of which were uncharacterized. The reactions were slowest in DME and were fastest in DMF and DMSO. The reactions in the latter two solvents required less intense irradiation. In general, the data obtained using the ethereal solvents were more consistent and reliable than that of DMF and DMSO.

Judging from the comparisons made above, THF seemed to be the most attractive solvent for testing a series of $S_{RN}1$ reactions. The first of this new series of reactions was that of 1 with potassio-2,4-dimethyl-

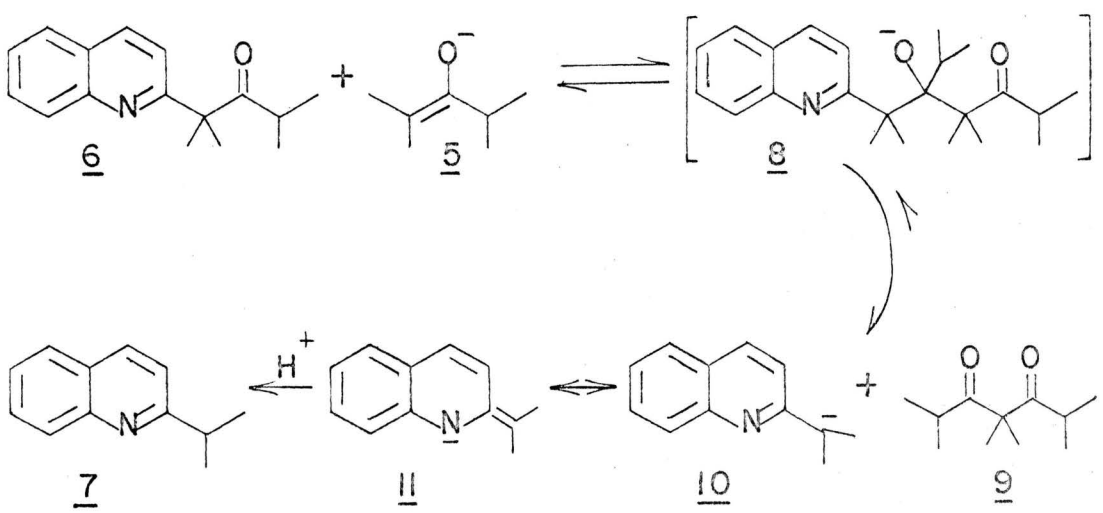
3-pentanone (5) as shown in equation 5. This reaction has been shown



(5)

to work well in liquid ammonia and to occur faster than the analogous reaction with potassioacetone.[13] When the reaction was carried out using a 1:3.75 ratio of 1 to 5, production of the expected substitution product 6 was accompanied by the formation of 2-isopropylquinoline 7. In the subsequent reactions of 1 with 5, a reduction of the ratio of 1 to 5 from 1:3.75 to 1:2 was made in order to retard the production of 7 which was thought to be formed by the mechanism shown in Scheme I.

SCHEME I

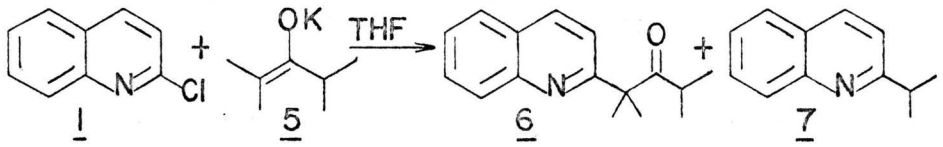


Here, intermediate anion 8, formed by the aldol condensation of anion 5 with 6, has three alternatives, either 1) to remain as it is; or 2) to reform 6 by expelling enolate anion 5; or 3) to expel the anion 10, thus forming the proposed β-diketone 9. The protonated analogue of 8 was not

observed, hence 8 is probably a short-lived intermediate if it is formed. From the data in Table III, it appeared as though the latter two alternatives were operating. The initial formation of 8 is probably an equilibrium process, while the conversion to 10 is essentially irreversible. This seemed reasonable because longer reaction times favored the conversion of 6 to 7 (compare experiments 1 and 4). Resonance stabilization of anion 10 in forms as 11 may explain its inability to readily add to the β-diketone, 9, to reform 8. Curiously, this side reaction does not seem to occur in liquid ammonia to a great extent. Hay and Wolfe[13] did report a reduction in their yields of 6 in liquid ammonia with increased reaction time, but it is not clear whether this loss is due to the formation of 7.

The other reaction systems that were tried in THF proved to be less complicated. Four different combinations of enolates and substrates which had been previously tried in liquid ammonia were tested in THF. Table IV shows the results of these reactions in THF and includes data for the closest corresponding reaction in liquid ammonia. Experiments 1 and 2 show only 33% and 64%, respectively, of 2-acetonylpyridine formed from the reaction of 2-bromopyridine with potassioacetone in THF after three hours of irradiation. In liquid ammonia, the identical reaction is complete in 15 minutes.[15] The reaction of iodobenzene with potassioacetone is essentially complete after three hours of irradiation in liquid ammonia,[26] but only a trace of phenylacetone is observed when the reaction is carried out in THF (experiment 3). Reactions with potassioacetophenone as a nucleophile are poor in both liquid ammonia

Table III[a]



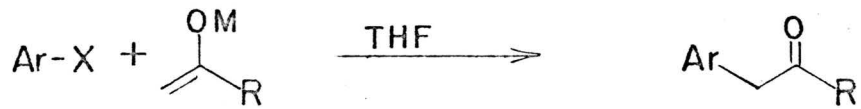
Expt. No.	Time(h)	Condition[b]	% Composition[c] 1	6	7
1	1.0	i	2	65(94)	25
2	1.0	i,DTBN	37	44	9
3	0.5	i	3	78	10
4	0.25	i	4	85(98)	7
5	0.25	i,DTBN	83	15	--
6	0.25	Dk	39	40	--
7	0.25	Dk,DTBN	78	17	--

[a]The molar ratio of 1 to 5 used in these experiments was 1:2.

[b]i (low intensity) indicates irradiation between 350-750 nm. DTBN represents the radical inhibitor di-t-butyl nitroxide. Dk represents a dark reaction.

[c]The percentages were determined by gas chromatographic analyses using the internal standard method.[20] Numbers in parentheses represent yields in liquid ammonia (reference 13).

TABLE IV



Expt. No.	Ar-X	R	M	Conditions[a]	% Composition[b] Ar-X	% Composition[b] Product
1	2-bromopyridine	CH_3	K	I,1.0(I,0.25)[c]	66	33(100)[c]
2	2-bromopyridine	CH_3	K	I,3.0(I,0.25)[c]	36	64(100)[c]
3	iodobenzene	CH_3	K	I,2.0(I,3.0)[d]	~Quant.	trace(67)[d]
4	2-chloroquinoline	C_6H_5	K	i,2.5(I,3.0)[e]	Quant.	0(14)[e]
5	2-chloroquinoline	CH_3	Li	i,10.0(I,1.0)[f]	17(18)[f]	14(48)[f]

[a]Intensity, reaction time in hours. I and i represent high intensity and low intensity irradiations, respectively. The data in parentheses represent that of the closest corresponding experiment in liquid ammonia.

[b]The percentages given were determined by gas chromatographic (GC) analysis using the internal standard method.[20] Data in parentheses are GC yields from liquid ammonia experiments.

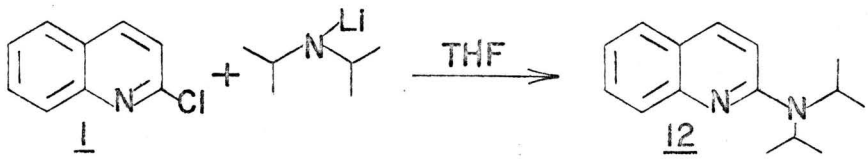
[c]Reference 15.

[d]Reference 26.

[e]Reference 13.

[f]Reference 12.

and THF. In each experiment the yields obtained from the reactions are consistent with the general observation that $S_{RN}1$ reactions are slower in THF than they are in liquid ammonia. The last experiment, 5, is interesting in that the major product observed was N,N-diisopropyl-2-aminoquinoline (12) which probably arises from the nucleophilic attack (not necessarily $S_{RN}1$) of lithium diisopropylamide upon 1 as shown in equation 6. It is conceivable that 12 could also arise from nucleophilic attack on 1 by diisopropylamine.



1 12 (6)

From the foregoing discussion, it is apparent that heteroaromatic $S_{RN}1$ reactions can be conducted in THF, DME, DMF, and DMSO with varying success. There are certain trends in the behavior of these reactions as the solvent is changed. Thus, the relative rates of reaction in these solvents increase as follows: benzene ≃ ether < DME < THF < ammonia < DMF < DMSO. The occurrence of dark reactions which appear to be $S_{RN}1$ in character, and the lack of effectiveness of radical inhibitors to prevent reaction is most evident in DMSO > DMF > THF > DME > ammonia. Some possible explanations are given for these observed trends.

The solvents used for this research and some of those used by Bunnett and co-workers[5] in their study are listed in Table V in the order of increasing dielectric constant. It is to be noted that the relative order of reaction rates in the solvents for heteroaromatic $S_{RN}1$ reactions is identical to the relative order of dielectric constants.

TABLE V

Some Physical Constants for Certain Solvents.

Solvent	$\varepsilon(^0C)$[a]	Donor Number[b]	UV %T Range[d]
Benzene	2.275(25)	14.9[c]	282 - 345
Diethylether	4.335(20)	19.2	230 - 313
DME	7.20 (25)	...	
THF	7.58 (25)	20.0	250 - 313
Ammonia	16.9 (25)	34.0[c]	215 - 225[e]
	23.0 (-33)		
HMPA	30.0 (20)	38.8	
Acetonitrile	36.2 (25)	14.1	213 - 250
DMF	35.71(25)	26.6	270 - 333
DMSO	46.68(25)	29.8	278 - 400

[a]Dielectric constants obtained from reference 27.

[b]Data taken from reference 28.

[c]Calculated value.

[d]Data determined from that in reference 29. Range: nm 50%T - nm 100%T.

[e]Data determined from that in reference 30.

Dielectric constants are related to the solvents' ability to ionize solutes. Since these reactions are faster in solvents with high dielectric constants, then the presence of charged intermediates (e.g., radical anions) which would be solvated by the polar medium is supported. The faster rates observed may be explained in terms of polarizable transition states which are readily solvated by the medium.[31] A correlation with dielectric constant would seem to be sufficient to predict the relative reaction rates in diverse solvents; however, this is not so. Bunnett and co-workers[5] found that HMPA, which has a high dielectric constant, was one of their poorest solvents. Acetonitrile, which should be a good solvent based on dielectric constant, did not allow reactions to proceed faster than they did in liquid ammonia which has a lower dielectric constant. Thus, dielectric constant alone is not sufficient to explain these solvent related relative reactivities.

Another possible effect on the reaction rate could be the solvent's ability to solvate the reactive species. Solvation ability has been correlated with several different physical parameters to generate polarity scales such as Kosower's Z scale,[24] Brownstein's S factor,[33], Berson's Ω,[34] or Grundwald's and Winstein's Y values.[35] All of these scales and a few additional ones are reviewed in texts by Leffler and Grundwald[36] and by Coetzec and Ritchie.[37] The main problem with most of these polarity factors was that they did not usually cover a sufficiently broad range of solvents or they were limited to only a particular type of solvent.

Among these polarity scales, Gutmann's donor number was thought to

be particularly suited to these solvents and their values are given in Table V. Gutmann's donor number is defined as the negative heat of reaction of the solvent with a molar equivalent of antimony pentachloride in an inert medium.[28] This number is an indication of the solvent's ability to either donate electrons to the cation (cation solvation) or accept electrons from the anions (anion solvation). In the solvents presently studied, cation solvation is operating to either enhance the formation of and stabilize polarizable transition states or increase the reactivity of "cation-free" nucleophiles.

The concept of the solvent's donating power may be extended to explain the greater extent of dark $S_{RN}1$ reactions observed in the more polar solvents as DMF and DMSO. Once the cation is solvated, it is conceivable that the excess solvent molecules could stimulate electron transfer from the nucleophile to the substrate because of its donating power. Equally likely, there could be a direct electron transfer, which could be stimulated by the anions in the solvent, to the substrate from the solvent. These processes could occur more extensively in solvents of higher donor number, or in other words, solvents which have a greater tendency to donate electrons. Either the "solvent induced" electron transfer from the nucleophile to substrate or the "nucleophile-induced" electron transfer from the solvent to substrate would be independent of photostimulation but could definitely be aided by it.

This theory could also explain the decreased effectiveness of radical scavengers in these polar solvents. With so many stimulated electron transfers occurring from the solvent molecules to, possibly, either

substrates or anions, or, even to other solvent molecules, small percentages of radical scavengers could be depleted rather quickly. In addition, shorter reaction times for substitution in DMSO and DMF may be explained in terms of the additional "solvent-induced" or "nucleophile-induced" initiations.

The problems with this proposed theory are its inability to explain why reactions in ammonia and HMPA, which have the largest donor numbers, are not the fastest of the solvents examined. It also fails to explain why acetonitrile, which has a low donor number and observed by Bunnett and co-workers to be a reasonable solvent for $S_{RN}1$ reactions, is as good as it is. Certainly, some combination of effects is operating. If a solvent's donating power is strongly temperature dependent, then liquid ammonia's lower capacity to stimulate these reactions in the absence of photostimulation may be due to the low (-33°C) reaction temperature. One could also rationalize its lower propensity toward dark reactions in terms of liquid ammonia's low dielectric constant. HMPA should be one of the best solvents for $S_{RN}1$ reactions based on dielectric constants and donor number. Its observed ineffectiveness must be due to some other factor.

The UV data given in Table V gives the percent transmittance ranges from where the solvent transmits more light than it adsorbs up to that wavelength at which all light is transmitted. The only correlation observed was that the solvents found to allow appreciable dark reactions (DMSO, DMF, and THF) also possessed some UV adsorption in the wavelength region 300-400 nm. This is the wavelength region that most of the

photostimulations were performed. This observation seemed to indicate that those solvents possessed the capacity for molecular excitation at the energy levels required to stimulate $S_{RN}1$ reactions of heteroaromatics. Ammonia does not have transition in this region, which suggests that no "solvent-induced" (see above) stimulation could occur in this solvent.

Upon re-examination of the data in Table II, one may note a marked decrease in reaction rate when the anion generating base was changed from potassium hydride to t-BuOK. This decrease in rate may be explained by the presence of t-butyl alcohol, which is generated upon forming an anion with t-BuOK, in the reaction mixture. Parker states that pure DMF and DMSO solutions are highly structured.[31] Traces of this alcohol in DMSO may lead to the formation of less structure solutions similar to that proposed[31] for DMSO-water solutions. It is possible that the way in which these solvents interact with $S_{RN}1$ reactants is impeded by water or alcohol impurities and requires the more highly structured medium for a more effective reaction. This may account for the slower rate observed in DMSO and, assuming a stronger effect in HMPA, that solvent's poorer capacity to serve as a medium for $S_{RN}1$ reactions.

An additional factor that could account for the observed variance in reaction rates in the solvents is their relative hydrogen atom donating ability. The reactions of both 2-chloroquinoline and iodobenzene with potassioacetone have been shown to proceed well in liquid ammonia.[13,26] However, the reaction in THF of iodobenzene with this anion is poor (see Table IV, expt. 3) whereas the analogous reaction with 2-chloroquinoline

in THF (see Table I, expt. 1) proceeds well. Phenyl radicals have been shown to be better hydrogen atom abstractors than quinolyl radicals under the conditions for $S_{RN}1$ reactions in liquid ammonia.[38] Since THF is a better hydrogen atom donor than liquid ammonia, it is conceivable that it could retard or inhibit the $S_{RN}1$ reactions of phenyl halides because of its ability to trap the phenyl radical intermediates.

Conclusions

The $S_{RN}1$ reaction of 2-chloroquinoline (1) with potassioacetone was studied in several solvents. THF, DMF, DMSO, and DME were found to be more suitable as solvents for this reaction than were diethyl ether and benzene. This reaction was stimulated by near UV irradiation and was inhibited by catalytic amounts of radical scavengers. Substantial reaction occurred during the dark reactions of 1 with potassioacetone in the more polar solvents, such as DMF. However, the $S_{RN}1$ character of these latter reactions was shown by inhibition studies.

The reactions conducted in DME were slowest and those of DMF were fastest. The overall desirability of DMSO as a solvent for this reaction was hindered by the sporadic nature of the results obtained in this medium. Of the solvents tested, THF was considered to be the most convenient for synthetic applications because the reactions in this solvent proceeded at a reasonably fast rate and were less hampered by side product formation. This solvent was also easiest to purify and to work with.

The $S_{RN}1$ reactions in THF of other heteroaromatic and carboaromatic systems were compared to their analogous reaction in liquid ammonia. It was found that in all cases the reactions in THF were slower. The change

in solvent slowed the reactions of the carboaromatic halides more than those of the heterocycles, which are known to be more reactive.[15] The reaction of 1 with potassio-2,4-dimethyl-3-pentanone (5) in THF was accompanied by a cleavage reaction that was observed to occur more readily in this solvent than in liquid ammonia.

The observed differences between the way these reactions behave in the different solvents is related to its overall solvent character. The relative contribution of each of the solvent properties to the overall character of the solvent is unknown. Of the properties discussed, solvation capacity would seem to be the most important, since it is known that increased polarization of reactants in anion reactions generally enhances their reactivity.[39] By necessity, this ability to solvate must be related to the solvent's dielectric constant. Its polarity would determine the solvent's ability to enhance or diminish the action of certain impurities. The effects caused by a solvent's ability to transmit or adsorb ultraviolet light or to trap radicals by hydrogen atom donation cannot be overlooked. Other properties, such as dipole moments, could also influence the overall solvent character. Nevertheless, it is clear that these properties are strongly inter-related in some way to give each solvent its unique characteristics which make it more or less suitable as a medium for $S_{RN}1$ reactions.

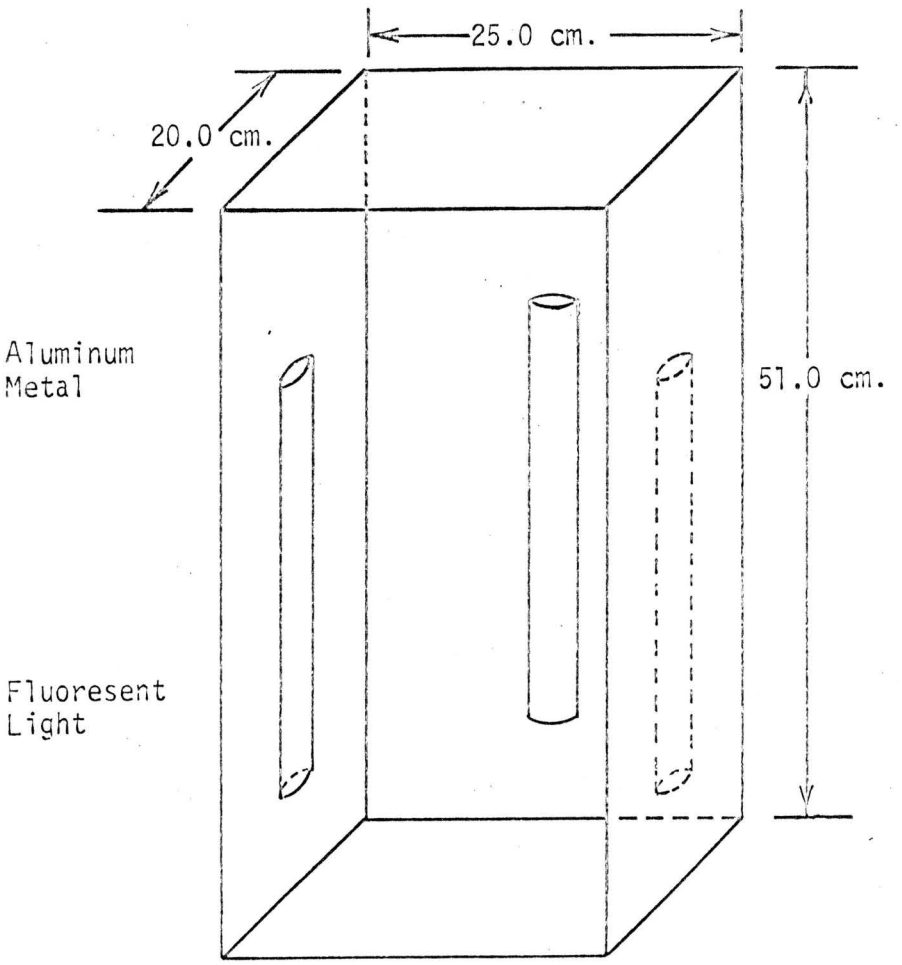
Experimental Section

All reactions were conducted under an atmosphere of nitrogen. The low intensity (350-750 nm)[18] photostimulated reactions were performed, using standard Pyrex round-bottomed flask, in the "Butina Reactor" (see

Figure I), produced in these laboratories by Dr. Darko Butina, postdoctoral research associate (1975). For the higher intensity (300-350 nm) photoreactions, a Pyrex vessel (see Figure II) containing the solution was immersed in a Rayonet RPR-240 photochemical reactor[19] which possessed four 12.5 W bulbs emitting maximally at 350 nm. Dark reactions were conducted in a darkened laboratory using standard Pyrex glassware wrapped with aluminum foil or a black shroud.

Gas chromatographic (GC) analyses and separations were accomplished on Varian Associates 90-P or 1200 instruments using columns of 2.5, 7.5, or 10% Carbowax 20M on Chromosorb G-HP or Chromosorb W-HP and operating between 150 and 225°C. GC yields were determined by the internal standard method[20] and quinoline, 4-methylquinoline, diallylphthalate, and dibutylphthalate were employed as internal standards. ^{1}H NMR spectra were determined on a JEOL JMN-PS-100 spectrometer at 100 MH_z using tetramethylsilane as a reference. Infrared spectra were produced on a Beckman IR-20A-X spectrophotometer. Microanalyses were determined in this department by Constance D. Anderson, Jorge I. Bedia, Elizabeth K. Cassity, T. E. Glass, or Roger W. Stringham on a Perkin-Elmer 240 elemental analyzer. Melting points were observed on a Thomas-Hoover apparatus and are uncorrected.

Tetrahydrofuran (THF) was refluxed over lithium aluminum hydride several hours prior to distillation. Dimethoxyethane (DME) was refluxed over sodium hydride and fractionated several times through a glass-helices packed column. Calcium hydride was used to dry dimethylformamide (DMF) and to initially dry dimethyl sulfoxide (DMSO) before their

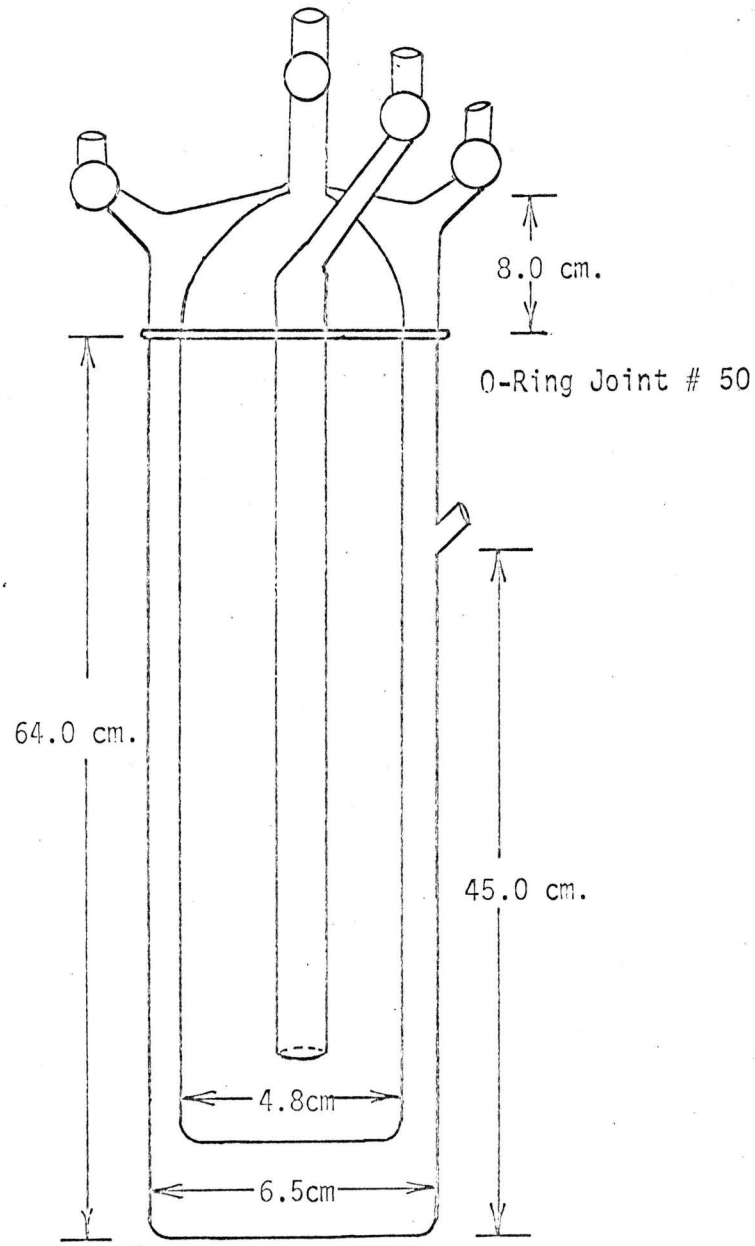


BUTINA REACTOR

FIGURE I

DESIGN: Darko Butina

REALIZATION: Darko Butina



PHOTOLYSIS REACTION VESSEL

FIGURE II
DESIGN: Subrata Chatterjee
REALIZATION: Andrew Mollick

distillation at reduced pressure. DMSO was further purified by treatment with sodium amide and distillation under vacuum.[40] All purified solvents were stored in bottles under argon atmosphere and over molecular sieves. Commercial potassium t-butoxide was sublimed prior to use. 2-Bromopyridine was distilled from barium oxide and 2-chloroquinoline was fractionated at reduced pressure. KH and all other chemicals were used without further purification.

The experiments described below are representative and serve as examples for conducting any of the reactions in this chapter.

Low Intensity Photostimulated Reactions of 2-Chloroquinoline (1) with Potassioacetone in DMSO

A 24% suspension of KH in mineral oil (3.13g, 18.75mmol) was weighed into a 125 ml round-bottomed flask equipped with a teflon stirring bar and an inlet and an outlet for nitrogen. The mixture was washed with hexane and upon settling (about 0.5 h) of the solid, the hexane solution was removed. The system was flushed with argon prior to the transfer of about 70 mL of DMSO through a canula from the solvent container to the reaction flask. The frothy mixture was stirred for about 15 min before acetone (1.5mL, 20 mmol) was added. The set-up, containing the resulting clear, yellow anion solution, was transferred to the illuminated "Butina Reactor" (see Figure I). Addition of 1 dissolved in DMSO produced a bright red mixture which darkened with time. After 15 min, 5-10 mL of water was added to quench the reaction. Approximately 300 mL of water was added to further dilute the mixture which was then extracted several times with ether. The combined extracts were dried with $MgSO_4$,

filtered, and concentrated under aspirator vacuum to give a crude orange solid. Recrystallization from aqueous ethanol yielded 0.29g (32%) of the yellow solid, 2-acetonylquinoline (2): mp 75-75.5°C (lit.[41] mp 76-77°C); IR ($CHCl_3$)$_\nu$ 1730 cm^{-1} (C=O); ^1H NMR ($CDCl_3$)δ 2.28 (s, 2.4 H, enol CH_3), 2.41(s, 0.6H, keto CH_3) 4.24 (s, 0.4H, keto CH_2), 5.38 (s, 0.8H, enol vinyl), 6.60-8.16 (m, 6H, aromatic), and 15.3 (broad s, 0.8H, enol). Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.71; H, 5.70; N, 7.51.

Inhibited Low Intensity Photostimulated Reaction of 1 with Potassioacetone in THF

A 24% dispersion of KH in mineral oil (6.35 g, 37.5 mmol) was weighed into a 250 mL round-bottomed flask equipped with a teflon coated magnetic stirring bar and an inlet and an outlet for nitrogen. The mixture was washed with hexane and after the solid had settled (about 0.5 h) the hexane solution was removed. The system was flushed with nitrogen prior to the transfer of about 125 mL of THF to the reaction flask. Acetone (3 mL, 37.5 mmol) was added slowly to suspension. Vigorous hydrogen evolution was observed and measured (1.1 L) with a gas buret. The pale yellow anion solution was transferred to the illuminated "Butina Reactor" (see Figure I). Addition of a THF solution of 1 (1.64 g, 10 mmol) and pDNB (0.084 g, 0.5 mmol) followed. After 1 h, the intensely dark solution was quenched with a small amount of water, 4-methylquinoline (0.332 g, 2.3 mmol) was added as an internal standard for GC analysis. The aqueous layer was separated and extracted with ether. The ether extracts and the THF layer were combined, dried with $MgSO_4$

filtered, concentrated under aspirator vacuum, and finally, analyzed by GC. Results: 2-chloroquinoline (1), 8.91 mmol (89%) and 2-acetonylquinoline (2) 0.14 mmol (1%).

Inhibited Dark Reaction of 1 with Potassioacetone in DMF

A 24% dispersion of KH in mineral oil (3.13 g, 18.75 mmol) was weighed into a 125 mL flask equipped with a teflon coated magnetic stirring bar and an inlet and an outlet for nitrogen. The mixture was washed with hexane and while the solid was settling, the solution was cooled in an ice bath. The hexane was removed and replaced with about 65 mL of DMF. The cloudy solution was stirred until it became clear and acetone (1.5 mL, 18.75 mmol) was slowly added. The solution was allowed to return to room temperature and the flask was wrapped in aluminum foil. After extinguishing the room lights and closing the shades, a solution of 1 (0.82 g, 5 mmol) and di-t-butyl-nitroxide (0.04 g; 0.28 mmol) in DMF was added to the flask. The mixture was quenched after 15 min with a little water and 4-methylquinoline (0.148 g, 1.03 mmol) was added as an internal standard. The solution was diluted with about 300 mL of water and extracted several times with ether. The ether extracts were combined, dried with $MgSO_4$, filtered, concentrated under aspirator vacuum, and analyzed by GC. Results: 2-chloroquinoline (1) 3.69 mmol (74%) and 2-acetonylquinoline (2) 0.38 mmol (8%).

Dark Reaction of 1 with Potassioacetone in DMSO

Freshly sublimed potassium t-butoxide (2.1 g, 18.75 mmol) was quickly weighed into a 125 mL round-bottomed flask equipped with a teflon coated stirring bar and an inlet and an outlet for nitrogen. The

flask was flushed with argon and about 65 mL of DMSO was transferred through a canula to the reaction flask. After about 15 min, acetone (1.5 mL, 18.75 mmol) was added to the stirred solution. The flask was wrapped in aluminum foil and also draped with a black shroud. The room lights were extinguished and a solution of 1 (0.82 g, 5 mmol) in DMSO was added. After 1 h, water was added to quench the reaction and 4-methylquinoline (0.113 g, 0.79 mmol) was added as a GC standard. The mixture was diluted with about 300 mL of water and extracted with ether several times. The ether extracts were combined, dried with $MgSO_4$, filtered, concentrated under aspirator vacuum, and analyzed by GC. Results: 2-chloroquinoline (1) 1.48 mmol (30%) and 2-acetonylquinoline (2) 1.99 mmol (40%).

Low Intensity Photostimulated Reaction of 1 with Potassioacetone in DME

A 24% dispersion of KH in mineral oil (3.13 g, 18.75 mmol) was weighed into a 125 mL flask equipped with a teflon coated magnetic stirring bar and an inlet and an outlet for nitrogen. The mixture was washed with hexane and after the solid had settled, the hexane was removed and replaced with about 70 mL of DME. While stirring the solution, acetone (1.5 mL, 18.75 mmol) was slowly added as vigorous hydrogen evolution was observed. The flask was transferred to the illuminated "Butina Reactor" (see Figure I) after which 2-chloroquinoline (0.82 g, 5 mmol) dissolved in DME was added. The intensely orange solution was quenched with a small amount of water after 1 h. The aqueous layer was extracted with ether. The ether extracts and the DME layer were combined, dried with $MgSO_4$, filtered and concentrated under aspirator vacuum. Preparative

gas chromatography of the mixture produced several previously characterized components including 2-chloroquinoline (1), 2-acetonylquinoline (2) and quinaldine. 2-methoxyquinoline was isolated as a colorless oil: IR (Neat)ν 1020, 1110 cm^{-1} (C-O). ^1H NMR ($CDCl_3$)δ 4.04 (s, 3H, OCH_3), 6.78-7.88 (m, 6H, aromatic).

1-Methoxy-2-quinoloxy ethane was isolated as a pale yellow oil: IR (Neat)ν 1045, 1110 cm^{-1} (C-O). ^1H NMR ($CDCl_3$)δ 3.45 (s, 3H, CH_3), 3.80 (m, 2H, CH_2), 4.64 (m, 2H, CH_2), 6.88-7.96 (m, 6H, aromatic). Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.34; H, 7.31; N, 6.76.

Low Intensity Photostimulated Reaction of 1 with Potassio-2,4-dimethyl-3-pentanone (5) in THF

A 24% dispersion of KH in mineral oil (6.35 g; 37.5 mmol) was washed with hexane in a 250 mL round-bottomed flask equipped with a teflon coated magnetic stirring bar and an inlet and an outlet for nitrogen. After the solid had settled, the hexane solution was removed and replaced with about 125 mL of THF. While stirring the solution, 5 (5 mL, 37.5 mmol) was added and the slow (about an hour) anion formation, as detected by H_2 evolution, was monitored with a gas buret. The reaction flask was placed in the illuminated "Butina Reactor" (see Figure I) and 1 (1.6 g, 10 mmol) dissolved in the THF was added. The reaction was quenched after 2.5 h with a little water. The aqueous layer was extracted with ether and these extracts were combined with the THF layer. The ethereal solution was dried with $MgSO_4$, filtered, and concentrated. Preparative GC on part of the concentrate afforded a

colorless oil, 2-(2-propyl)quinoline (7) ^{1}H NMR (CCl_4)δ 1.42 (d, 6H, CH_3), 3.26 (sept, 1H, CH), 7.2-8.1 (m, 6H, aromatic). Anal. Calcd. for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N. 8.18. Found: C, 84.50; H, 7.73; N, 10.45.

The desired substitution product 6 was also isolated by preparative GC. Chromatography on silica gel eluting with ethyl acetate afforded crude 6, which was recrystallized from aqueous ethanol yielding 0.52 g (22%) of white needles mp 93-94°C: IR(CCl_4)ν 1710 cm^{-1}(C=O). ^{1}H NMR (CCl_4)δ 0.88 (d, 6H, CH_3), 1.56 (s, 6H, CH_3), 2.62 (sept, 1H, CH), 7.02-7.82 (m, 6H, aromatic). Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.63; H, 7.93; N, 5.81. Found: C, 79.67; H, 7.73; N, 5.70.

High Intensity Photostimulated Reaction of 2-Bromopyridine with Potassioacetone in THF

A 22% dispersion of KH in mineral oil (6.84 g; 37.5 mmol) was washed with hexane in the photolysis reaction vessel shown in Figure II. After the solid had settled, the hexane was removed and the vessel was flushed with argon. Transfer of about 125 mL of THF through a canula to the reaction vessel was done. The vessel was kept under a positive pressure of nitrogen. The cold-finger water connections were checked.[42] Acetone (2.76 mL; 37.5 mmol) was slowly introduced and washed in with additional THF. The vessel was lowered into the photolysis chamber and irradiation was begun. 2-Bromopyridine (1.58 g; 10 mmol) dissolved in THF was then added and the timing was begun. After 3 h of irradiation, the orange solution was quenched with about 10 mL of water. Quinoline (0.235 g; 1.82 mmol) was added as internal standard. The aqueous layer was extracted with ether and these extracts were combined with the THF layer.

The organic solution was dried with $MgSO_4$, filtered, concentrated under aspirator vacuum, and analyzed by GC. Results: 2-bromopyridine 3.57 mmoles (36%) and 2-acetonylpyridine 6.39 mmole (64%).

Low Intensity Photostimulated Reaction of 1 with Lithioacetone in THF

A solution of diisopropylamine (2.03 g; 20 mmole) in 100 mL of THF under nitrogen was stirred and cooled in a dry ice-2-propanol bath. To this solution was added a 2.1 molar solution of n-butyl-lithium in hexane (9.5 mL; 20 mmole). After 15 min, acetone (1.09 g; 18.75 mmol) in THF was added to the cold solution and was stirred for 15 min to allow the anion to form. Irradiation in the "Butina Reactor" was begun and 1 (0.82 g; 5 mmol) in THF was quickly added to the cold solution. The solution was kept cold for 1 h and then allowed to reach room temperature. After 10 h, from the addition of 1, the mixture was quenched with water. Diallylphthalate (0.235 g; 0.97 mmol) was added as an internal standard for GC analysis. The aqueous layer was extracted with ether and these extracts were combined with the THF layer. The organic solution was dried with $MgSO_4$, filtered, concentrated under aspirator vacuum, and analyzed by GC. Results: 2-chloroquinoline (1) 0.87 mmole (17%), 2-acetonylquinoline (2) 0.82 mmoles (14%) and N,N di-2-propyl-2-aminoquinoline (12) 2.99 mmol (60%).

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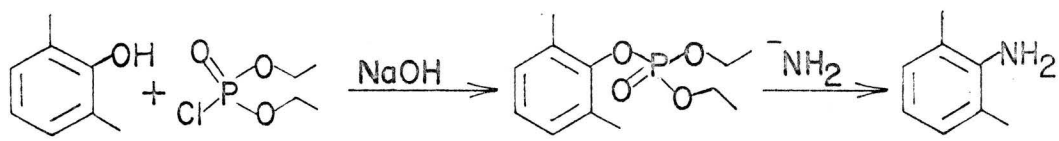
CHAPTER III

Synopsis: The effectiveness of cyanoalkyl and 4-picolyl anions as nucleophiles for heteroaromatic $S_{RN}1$ reactions is described.

Numerous nucleophiles other than ketone enolates have been tried as reactants in $S_{RN}1$ reactions of carboaromatic halides.[1,2] Among those that work, in this extensively explored area, are ester enolates[3], thiophenoxide ion[4,5], picolyl anions[6], diethyl phosphite anion[7], α-cyanoalkyl anions[8,9,10], and amide ion.[11,12] These findings have helped extend the practical usefulness of $S_{RN}1$ reactions to effect syntheses such as that shown in equation 1 for the conversion of a phenol to its corresponding aryl amine. Conversions such as those described above are not generally easy to accomplish by other synthetic routes.[12] In equation 1, the nucleofuge, or leaving group, for the $S_{RN}1$ reaction is diethyl phosphite ion.



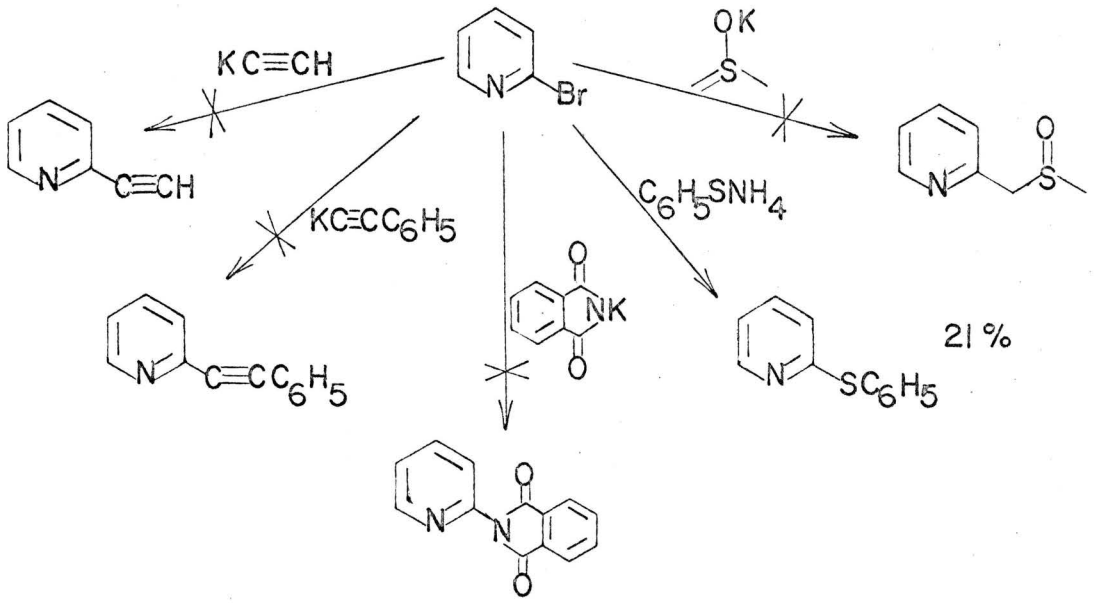
(1)

The amount of work reported in the literature concerning $S_{RN}1$ reactions of heterocyclic systems with non-ketone nucleophiles is quite limited. Zoltewics and Oestreich reported the $S_{RN}1$ reactions of thiophenoxide ion with 4-bromoisoquinoline.[13] Nucleophilic substitutions by amide ion on heterocyclic systems have been reported by van der Plas'[14] and Bunnett's[15] research groups. Recently, van der Plas employed potassium superoxide as a nucleophile for $S_{RN}1$ reactions with halogenated quinolines and isoquinoline.[16] Thus, many of the nucleophiles previously tried with carboaromatic halides had not been tried with heteroaromatic

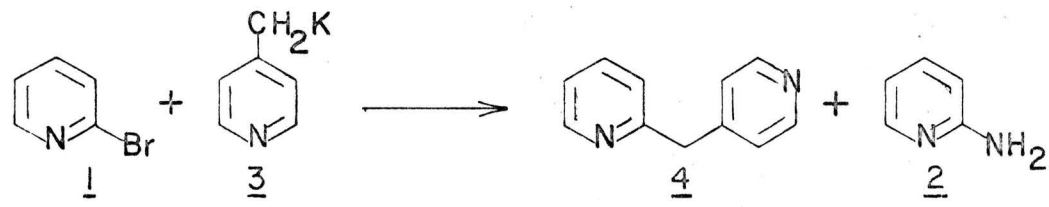
halides until work in this laboratory was begun.

Dr. A. P. Komin[17] explored the $S_{RN}1$ reactions of 2-bromopyridine (1) with several nucleophiles (Scheme I) and found that 1 was completely

SCHEME I

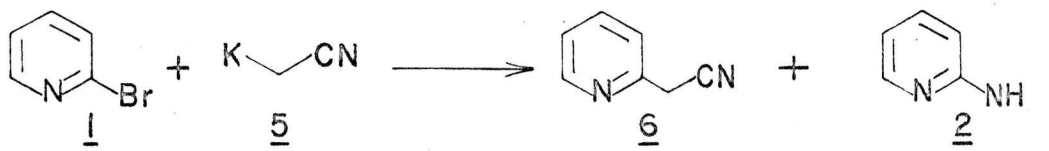


recovered upon treatment with the potassium salts of acetylene, phenylacetylene, and phthalimide after 2 hours of irradiation in liquid ammonia. Only 21% of 2-pyridylphenyl sulfide was observed after 1.5 hours of irradiating 1 and ammonium thiophenoxide. Unlike the previous four examples, the photostimulated reaction of 1 with dimsyl potassium consumed all of 1 in 15 minutes; however, the major product formed was 2-aminopyridine (2) instead of the desired substitution product, 2-pyridyldimethyl sulfoxide. The photostimulated reaction (equation 2) of 1 with 4-picolyl potassium (3) was more effective; affording 2,4'-dipyridylmethane (4) and 2-aminopyridine (2) in a ratio of 1:3 after 15



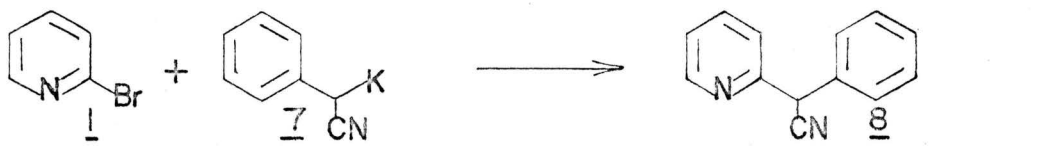
1 3 4 2 (2)

minutes. Similarly, the reaction of potassioacetonitrile (5) and 1 as shown in equation 3 gave a mixture of 75% of 2-pyridylacetonitrile (6)



1 5 6 2 (3)

and 16% of 2 after 15 minutes of irradiation. Subsequent reactions designed to retard the $S_{RN}1$ reaction by decreasing the amount of photostimulation, or by using radical inhibitors increased the yield of 2 at the expense of 6. Thus, the formation of 2 is undoubtedly occurring by an ionic process. The photostimulated reaction of 1 with potassiophenylacetonitrile (7) illustrated in equation 4 resulted in an 88% yield



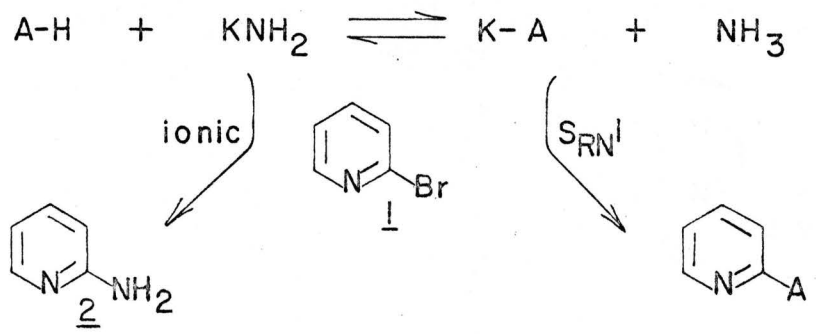
1 7 8 (4)

of the desired substitution product (8) with no 2 being detected. The corresponding dark reaction does not work.[17]

The last four results concerning the consumption of 1 to form its aminated analogue, 2, can be explained in terms of the relative pKa differences between ammonia and the protonated nucleophiles. Even though the pKa values for phenylacetonitrile, acetonitrile, and dimethyl sulfoxide (DMSO) in ammonia are not known, the values obtained by

Bordwell and co-workers[18,19] in DMSO (21.9, 31.3, and 35.1, respectively) may indicate the order of acidity in ammonia. The pKa of 4-picoline in ammonia is 29[20] and approaches that of ammonia in ammonia, 32.5.[21] Thus, there is an appreciable equilibrium concentration of amide ion present when potassium amide is used to generate anions 3, 5, and dimsyl potassium. This equilibrium accounts for the series of competing reactions shown in Scheme II for these anions (A^-). In con-

SCHEME II

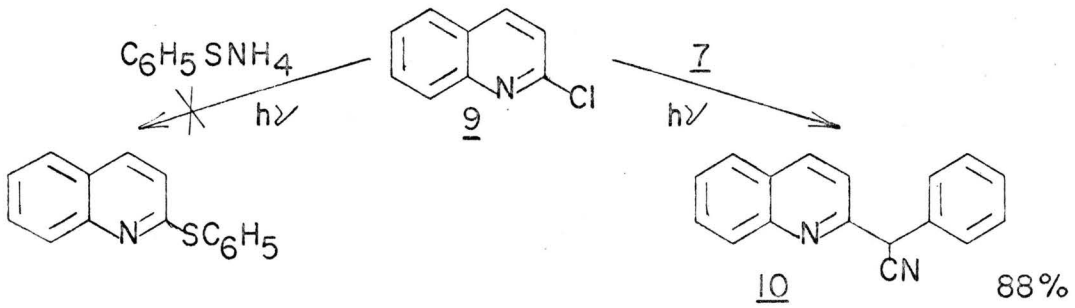


trast, phenylacetonitrile is much more acidic than acetonitrile, DMSO, or 4-picoline; therefore, there is not a significant equilibrium concentration of potassium amide present to compete with the $S_{RN}1$ reaction of 7.

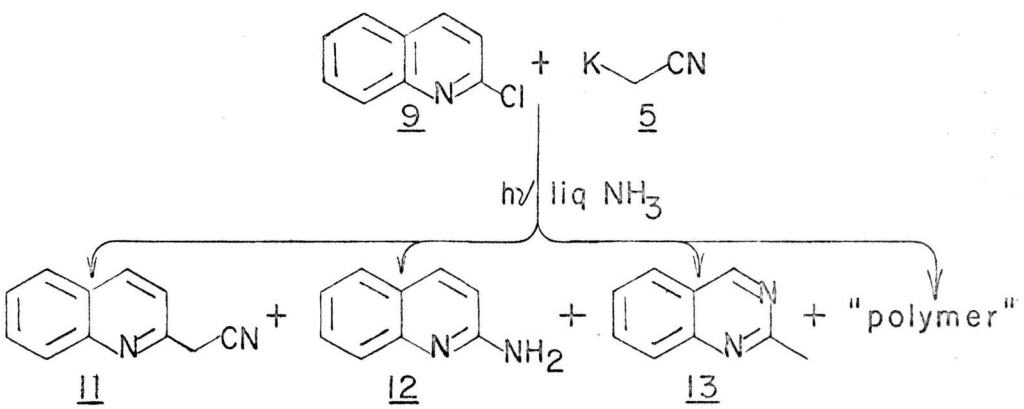
It has been observed that only very small amounts of aminated side products were formed during the reaction of 3 and 5 with halobenzenes.[4,6,8] The differences between the relative amounts of aminated products formed in the reactions of carboaromatic and heteroaromatic halides can be rationalized in terms of the lesser tendency for the halobenzenes to undergo benzyne or S_NAr2 reactions at rates competitive with their $S_{RN}1$ reactions.[17]

Results using 2-chloroquinoline (9) as a substrate were found to be similar to those obtained with 2-bromopyridine in some cases. The reaction of thiophenoxide with 9 resulted in an 83% recovery of 9 after 1.5 hours of irradiation in liquid ammonia. 2-Quinolylphenylacetonitrile (10) was isolated in 88% yield from the photostimulated reaction of 9 with 7 (Scheme III).

SCHEME III



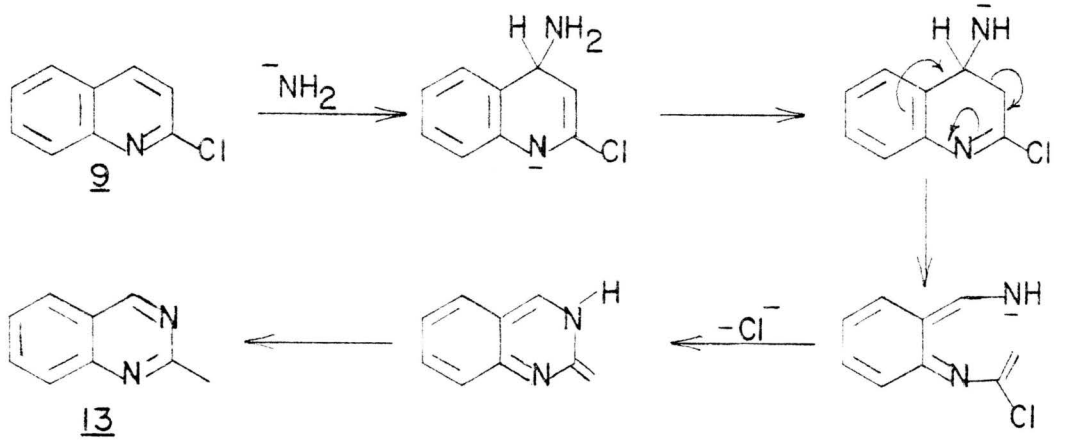
The reaction of 9 with potassioacetonitrile (5) was expected to give results similar to those observed from reactions of 1 with 5; however, other products were also formed (equation 5). In addition to the



(5)

expected 2-quinolylacetonitrile (11) and 2-aminoquinoline (12), there was found "polymer" along with 2-methylquinazoline (13).[17] The latter product, 13, was believed to arise from the S_N(ANRORC) type mechanism proposed by den Hertog and Buurman[22] and illustrated in Scheme IV.

SCHEME IV



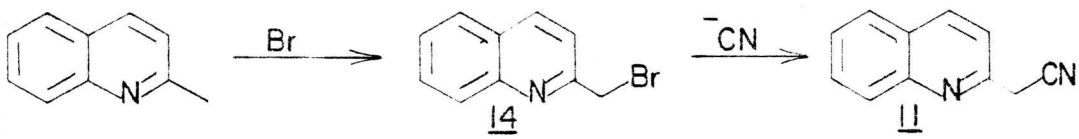
Discussion and Results

The present research was begun so as to complete the analysis of the reaction system given in equation 5. In order to complete the analysis, it was necessary to obtain authentic samples of 11, 12 and 13 for ascertaining their identity in the reaction mixture and for preparing gas chromatography (GC) standardization solutions. However, due to the complexity of typical reaction mixtures, it was not always possible to obtain each component in large enough quantities and sufficient purity for this purpose. In most cases, an independent method of synthesizing the presumed compound was done to check its identity and provide the necessary compounds for GC standards.

The two side products, 2-aminoquinoline (12) and 2-methylquinazoline

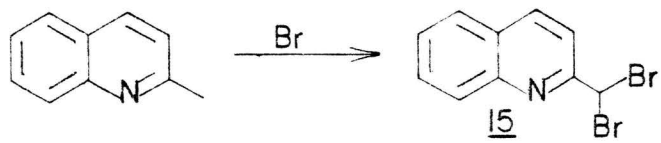
(13), given in equation 5, were prepared by known methods.[23,22]

Several procedures were tried for preparing 2-quinolylacetonitrile (11). The first of these was an attempted synthesis from quinaldine via the intermediate α-bromoquinaldine 14 (equation 6).



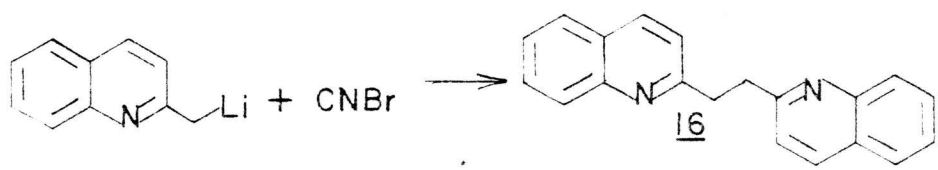
14 11 (6)

This preparation was not realized due to failure in attempts to isolate enough of lachrymatory 14 or its chloro analogue. The major product obtained from the bromination of quinaldine by numerous variations of two methods[24,25] was α,α-dibromoquinaldine (15).



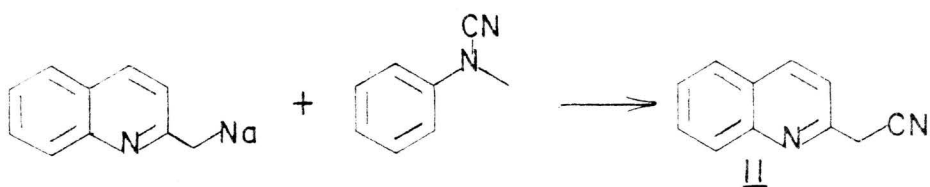
15

Attempts to synthesize 11 from α-lithioquinaldine and cyanogen bromide also failed. The major product obtained from this reaction (equation 7) was 2,3-di-(2'quinolyl)ethane (16) in 60% yield.



16 (7)

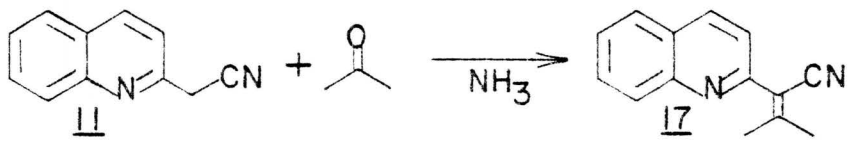
2-Quinolylacetonitrile (11) was finally synthesized by the procedure of Lettre, Jungmann, and Salfeld[26] as shown in equation 8. This method



11 (8)

involves nucleophilic attack of quinaldine anion upon the cyano group of N-methyl-N-cyanoaniline.

Preparative GC of one of the first reaction solutions resulting from the photostimulated reaction of potassioacetonitrile with 9 showed that 11 was present. However, the major component of the mixture was 3-methyl-2-(2'-quinolyl)-2-butenonitrile (17). This compound was isolated in 16% yield and undoubtedly arose from a Knoevenagel reaction (equation 9) of acetone and 11. Reactions of this type have been known



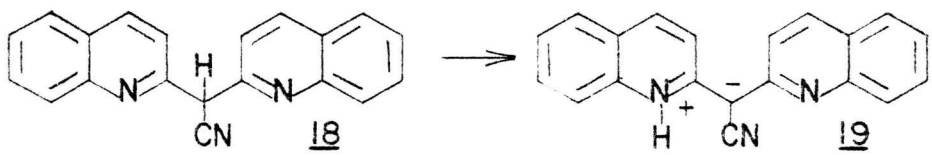
11 17 (9)

to readily occur with pyridylacetonitriles,[27] thus similar reactivity should be expected with quinolylacetonitriles. In the present example, acetone was the solvent used to solubilize the quenched reaction mixture and the residual ammonia was apparently a strong enough base to catalyze the condensation. The dehydration step to form the alkene 17 would be enhanced by the stabilization of the resulting double bond in conjugation with both the quinolyl and cyano functions. THF and DME were subsequently used to dissolve the reaction mixtures in the remaining experiments to avoid this side reaction.

The reaction illustrated in equation 5 was repeated several times. In each of the resulting reaction solutions, several different fractions of solid material could be triturated from the quenched reaction mixtures using varying amounts of ether. These broad-melting solids were believed to be "polymer" because of their generally broad infrared and

^{1}H NMR spectra. The structural units present in these fractions include aromatic rings and nitrile functions as deduced from those spectra. Attempts to determine a molecular weight range for these "polymers" by vapor pressure osmometry were hampered by their low solubility in THF and $CDCl_3$, the solvents that were used for these determinations.

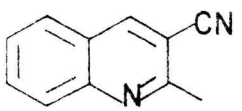
In addition to the products shown in equation 5, the $S_{RN}1$ reaction of 9 with 5 was found to produce disubstitution product 18. Judging



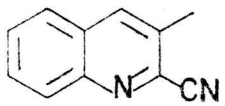
from its ^{1}H NMR spectrum and its high melting point (280-282°C) relative to that of 11 (50-52°C), 18 may exist predominantly as its zwitterion, 19. A structure such as 19 could also explain this compound's observed low solubility in THF, $CDCl_3$, and ether. Its solubility characteristics and the similarity of its IR spectrum to that of some of the "polymer" fractions leads one to conclude that this compound was probably a contaminant in some of the "polymer" fractions. Attempts to synthesize a lower melting derivative of 18 (19) by methylation with methyl iodide failed in the presence of triethylamine or even sodium hydride, presumably because of the steric bulk of the quinoline rings.

An unanticipated product, 3-cyano-2-methylquinoline (20) was also isolated from the reaction of 9 with 5. The general appearance of its ^{1}H NMR spectrum could be explained by a structure such as 2-methylquinazoline (13), and for some time compound 20 was thought to be 13. However, upon closer examination of its infrared and mass spectra it

became obvious that the compound had to be one of six possible cyanomethylquinolines (20-25). The compound isolated from the reaction

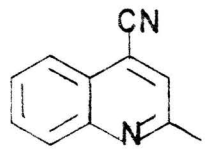


20



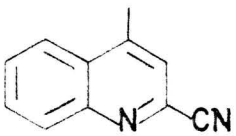
21

lit[28] mp 130-131°C



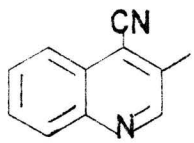
22

lit[29] mp 105-106°C

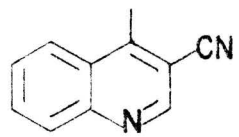


23

lit[29] mp 96-98°C



24



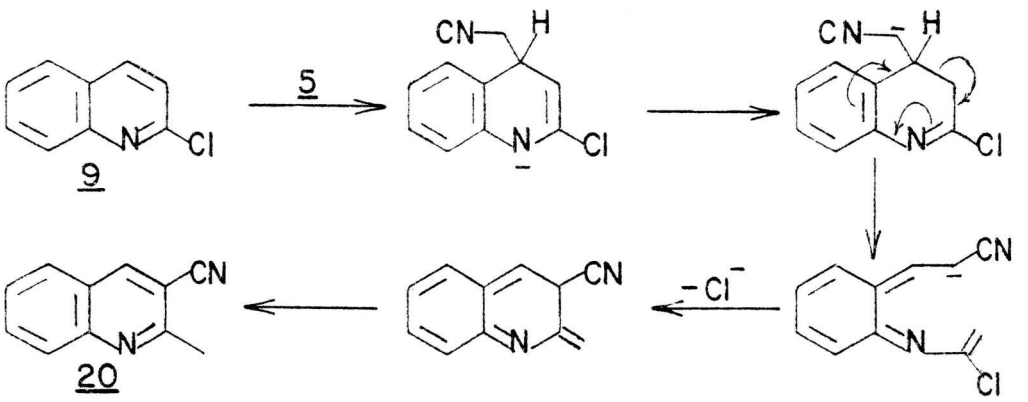
25

lit[30] mp 140-141°C

mixture had a melting point range of 129-130°C, thus compounds 22, 23, and 25 could be immediately ruled out based upon melting points. The ^{1}H NMR shift (8.44 δ) of the heteroaromatic ring proton of the isolated compound was at higher field than that expected for the 2-proton of 24 or 25.[31] In both cases this proton should be deshielded by the adjacent nitrogen.

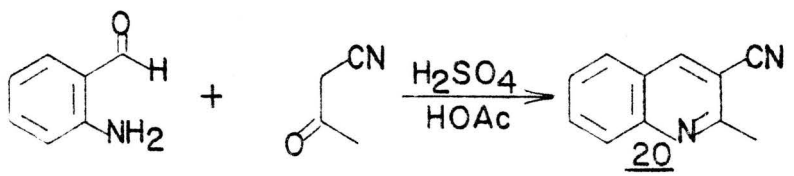
Attempts were made to rationalize the formation of 20 or 21, the remaining two possibilities. Neither isomer arose from a rearrangement of 11 since the latter compound was found to be stable in the presence of amide or acetonitrile anion under the reaction conditions. However, the possibility of an S_N(ANRORC) type reaction of 5 with 9, similar to that observed for amide ion with 9,[22] seemed attractive. If this mechanism were operating the sequence of steps in Scheme V would be followed

SCHEME V



and could explain the formation of 20. A mechanism for the production of 21 could not be formulated.

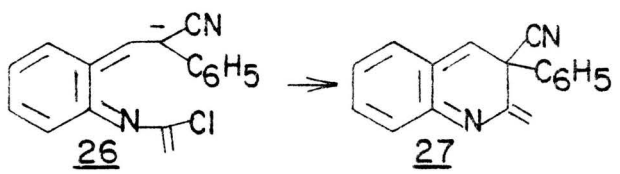
Scheme V provided a rationale for assigning structure 20 rather than 21 to the isolated compound, but more positive evidence was desired. Isomer 20 was synthesized by a modified Friedlander condensation[33] of cyanoacetone and o-aminobenzaldehyde as shown in equation 10.



(10)

The spectral characteristics of this authentic sample were identical to those of the isolated compound. Therefore, the isolated compound is 20.

Aromatization is probably the driving force for the reaction shown in Scheme V. The inability for an intermediate such as 27 to rearomatize



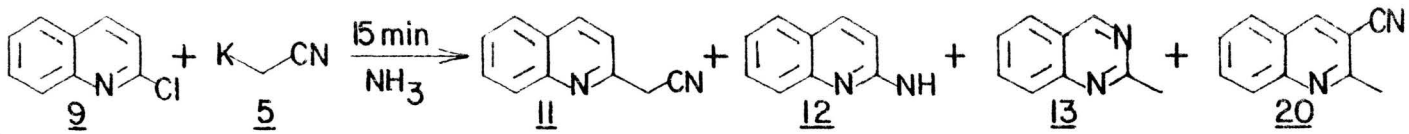
due to disubstitution at the 3 position may explain the absence of rearranged side products in the reaction of 9 with phenylacetonitrile anion (7) or other secondary anions. It is difficult to explain why such rearranged products were not observed with other primary anions such as acetone enolate.

Table I shows gas chromatography (GC) yields from 15 minute reactions of 9 with 5 in liquid ammonia under varying conditions. In each experiment all of 9 was consumed to afford the products given in Table I. In addition, a "polymer" fraction which precipitated from the concentrated reaction solutions was obtained. This fraction possibly contained some disubstituted product 18, (19) which would coprecipitate because of its known low solubility in THF. No quantitative determinations were attempted on these latter fractions.

Experiment 1 shows that a fair yield (50%) of 11 is obtained from the photostimulated reaction of 9 and 5. However, the overall result from experiments 2 and 3, in which the ratio of acetonitrile to potassium amide was increased, were progressively poorer. The dark reaction of 9 with 5 (experiment 4) produces a fair yield (37%) of rearrangement product 20 along with unmeasurable amounts of 11, 12, and 13. As with the photostimulated reactions, larger ratios of nitrile to amide ion in dark reactions discouraged the formation of all four products (experiments 5 and 6).

When these experiments were begun, compound 20 was erroneously assigned structure 13. Experiments 2, 3, 5, and 6 were originally designed to reduce the yields of the side products arising from the

TABLE I



Expt. No.	Conditions[a]	% Composition[b]			
		13	12	20	11
1	I,1:3.75:3.75	1	-	2	50
2	I,1:3.75:7.50	-	-	5	19
3	I,1:3.75:11.25	-	-	-	15
4	Dk,1:3.75:3.75	trace	trace	37	trace
5	Dk,1:4.5	-	-	18	4
6	Dk,1:3.75:7.50	-	-	9	3

[a] I represents a high intensity irradiation performed in a Rayonet RPR-240 photochemical reactor.[45] The ratio of 9: potassium amide: acetonitrile is given.

[b] The percentages were determined by GC analyses using the internal standard method.[46]

reaction of 9 with the equilibrium concentration of amide ion. By le Chatelier's principle, increasing the concentration of acetonitrile relative to that of amide ion should reduce the equilibrium amide ion concentration and thus reduce the formation of products due to amide ion reactions with 2. These changes gave poorer results than were obtained in the original reactions (Experiments 1 and 4).

In view of the correct assignment of structure 20, it can be concluded that the major problem with this reaction system does not concern the equilibria of acetonitrile and potassium amide, but rather reactions of intermediate anions with the excess acetonitrile. Aliphatic nitriles are known to undergo self condensations[34] or condensation with other nitriles[35,36] to form dimers, trimers, and larger systems. Therefore, it is conceivable that in these reaction systems, unionized nitrile compounds would be available for nucleophilic condensation to form uncharacterizable polycondensation products. Due to the apparent facility with which the postulated ring-opening side reactions of 9 with 5 (Schemes IV and V) occur, there is a good possibility that any of the transitory anion intermediates, found in such reactions, could condense with either acetonitrile, or any of the resulting condensation products. Hence, it seems reasonable to conclude that reaction mixtures less contaminated with "polymer" fractions would be obtained if measures are taken to minimize the amount of unionized nitrile compounds in solution.

The reaction of 9 with 5 is less complex when the reaction solvent is THF. An equivalent of potassium hydride was used to generate 5. After 1 hour of irradiation 31% of 11 and 9% of 20 was produced along

with the disubstituted compound 18. 2-Chloroquinoline (36%) remained unaltered after that time. In a similar 2-hour experiment, 18 was isolated by chromatography in 22% yield.

The results involving 5 and 9 should be compared to the photostimulated reaction of 5 and 2-bromopyridine, 1, in liquid ammonia. This reaction does not afford any appreciable amounts of either "polymer" or ring transformed products.[17] One may rationalize the latter observation in terms of the lesser reactivity toward nucleophilic attack of the pyridine ring's 4-position relative to that of quinoline. Ring transformations of 6-substituted-2-bromopyridines to their corresponding pyrimidines by means of potassium amide in liquid ammonia have been shown to require five minutes to two hours, depending on the substituent[37], whereas the more reactive 2-bromoquinoline is transformed to 2-methylquinazoline in about one minute under essentially identical reaction conditions.[22] Less negative charge density, as predicted by molecular orbital calculations,[38] at the 4-position of quinoline than there is at the 4-position of pyridine may explain quinoline's increased activation towards nucleophilic attack at that position. Since an appreciable amount of ring transformation is observed in the reactions of quinoline rather than pyridine, it seems reasonable to conclude that the "polymer" arises from unspecified reactions of the ring-opened intermediates leading to 13 and 20. Thus, the absence of similar ring-opened intermediates in the reactions of 1 may explain why no "polymer" forming reactions are observed.

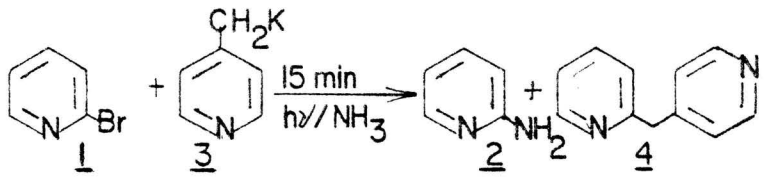
It was previously shown[17] that the $S_{RN}1$ reaction of 4-picoline

anion (3) and 2-bromopyridine 1 (equation 2) also had to compete with the ionic substitution reaction of 1 with amide ion. The reaction produced a 1:3 ratio of 4 to 2, the desired substitution product and 2-aminopyridine, respectively. Since 4-picoline possessed no reactive functional groups, it was felt that this system was ideal for testing the equilibrium hypothesis concerning competing aminations discussed earlier for the reaction of 9 with 5. An attempt to improve the yield of 4 by shifting the equilibrium toward 3 with excess 4-picoline was made.

Table II shows the results obtained from the reactions of 1 and 3 in which the ratio of amide ion to 4-picoline is varied. As the ratio of picoline to amide ion is increased (experiments 1, 2, and 3), the yields of 4 increase and the yields of 2 decrease. These observations are consistent with the expected results; however, experiment 4 was anomalous. Since the largest 4-picoline to amide ion ratio (2:1) was used in this experiment, one would have expected an even lesser equilibrium concentration of amide and thus higher yields of 4 and lower yields of 2.

Two explanations are offered for this observed difference. First, when the equilibrium is shifted toward the formation of 3, ammonia must be generated. Since ammonia is the solvent for this reaction, the large excess of this reagent present which would have a tendency to shift the equilibrium toward amide ion. In none of the experiments was the amount of ammonia used precisely determined. Therefore, there is a possibility that larger amounts of ammonia were used in experiment 4 than in the

TABLE II



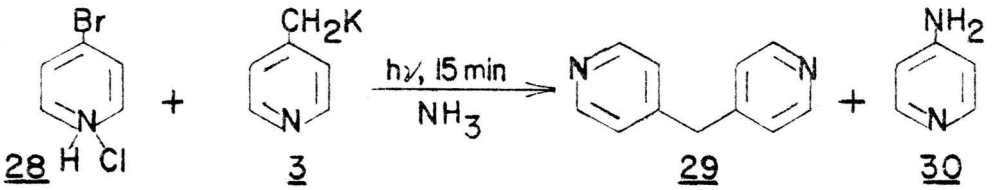
Expt. No.	Molar Ratios[a]	% Composition[b]	
		2	4
1	1:4:5	67	24
2	1:3.75:3.75	53	37
3	1:5:4	46	47
4	1:8:4	59	39

[a]The molar ratio of 1 to 4-picoline to potassium amide is given.

[b]Percentages were determined by gas chromatography using the internal standard method.[46]

others thus causing an increased amide ion concentration. Second, perhaps 4-picoline acts as a weak radical scavenger. Thus, large excesses of this reagent may tend to have an inhibitory effect on the $S_{RN}1$ reaction thereby allowing the ionic amination reaction to predominate. Other workers have observed no inhibitory-like character of 4-picoline in the $S_{RN}1$ reactions of carboaromatic halides.[6] Realistically, neither of these arguments is very satisfactory.

The reaction of 3 with 4-bromopyridine hydrochloride, 28, (equation 11) proved to be surprising. The desired substitution product, 4,4'-



(11)

dipyridylmethane (29) was produced in 78% yield along with less than 1% of 4-aminopyridine, 30. In contrast to the analogous reactions of 1 with 3, there was no significant amination side reaction. Unlike the reaction of 4-bromopyridine with potassioacetone, which afforded only 28% of 4-acetonylpyridine,[39] the reaction of 28 with 3 proceeds quite well. The major difference between the present reaction (equation 11) and the others just mentioned is that the hydrochloride salt of 4-bromopyridine was used directly.

The increased effectiveness of 28 over than of 4-bromopyridine in these reactions may be attributed to a temporary and instantaneous upsetting of the equilibrium between amide ion and 3. Part of that equilibrium involves the reaction of equation 12, which must be slower than the reverse reaction because 4-picoline is more acidic than

(12)

ammonia. Thus, when the hydrochloride 28 is added to the anion solution 4-bromopyridine is liberated but the generated hydrochloric acid is immediately quenched by the strongest base in solution. Any residual potassium amide would be neutralized before 3 would be. The $S_{RN}1$ reaction, therefore, probably occurs before the equilibrium between amide ion and 3 can be reestablished. Thus, the small amount of aminated side products observed would be due to a temporary reduction of available amide ion for reaction with 4-bromopyridine.

This hypothesis requires that the aforementioned $S_{RN}1$ reaction is faster than the proton transfer reaction of equation 12. Rates of proton transfers to carbanions have been observed in the range 10^1 to 10^6 in DMSO[40] and in aqueous solvents.[41] Eargle and coworkers determined the rate of the $S_{RN}1$ reaction involving biphenylyl iodide in THF-DME solution to be $4.2(10^6)$.[42] Recalling that the $S_{RN}1$ reactions of heteroaromatic halides tend to be faster than those of carboaromatic halides,[39] and that $S_{RN}1$ reactions in liquid ammonia proceed more rapidly than they do in THF or DME (Chapter II), it is not unreasonable that the $S_{RN}1$ reaction of 3 with 28 could be faster than the reaction of equation 12.

The synthesis of 29 by the described $S_{RN}1$ reaction is a more simple and a higher yield process than that reported earlier[43] which involved

the preparation and subsequent hydrazine reduction of bis(4-pyridyl) ketone.

Conclusions

$S_{RN}1$ reactions of 2-chloroquinoline and of 2- and 4-bromopyridines with 4-pyridyl and nitrile stabilized anions can be accomplished. However, determining the most effective reaction conditions requires a thorough consideration of the intrinsic peculiarities of each system.

The $S_{RN}1$ reactions of these heteroaromatic halides are faster than those of the halobenzenes.[39] However, these heterocycles are also more reactive toward benzyne and S_NAr2 side reactions that occur in the presence of equilibrium concentrations of amide ion present upon generating the anions of the nitriles and 4-picoline from potassium amide. In contrast, the $S_{RN}1$ reactions of halobenzenes are not as seriously affected by small concentrations of amide ion.[6,8,9,10]

Ring transformations are unique to the heteroaromatic systems and usually involve attack by amide ion. However, in this study, these transformations were found to be effected by acetonitrile anion as well. Reactions involving 2-chloroquinoline (9) were more susceptible to these transformations than were those involving the less reactive pyridines.

The high yield reactions of 2-chloroquinoline (9) with potassiophenylacetonitrile (7) or of 4-bromopyridine hydrochloride (28) with 4-picoline anion (3) by the $S_{RN}1$ mechanism are superior to the literature procedures.[44,43] But, because of the numerous side products obtained, the synthesis of 2-quinolylacetonitrile (11) by the $S_{RN}1$ pathway is not as desirable, synthetically. The reactions of 2-bromopyridine (1) with

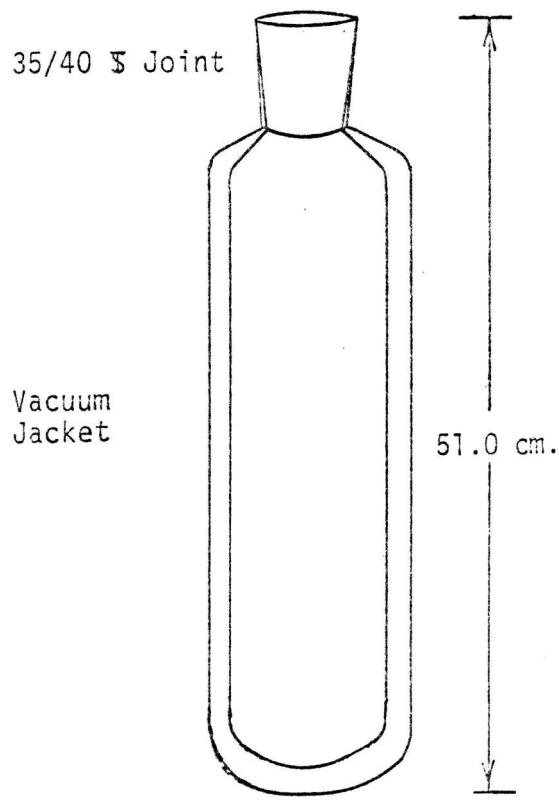
acetonitrile and 4-picoline anions might be improved by employing the hydrochloride salt of 2-bromopyridine in a manner similar to that used for the $S_{RN}1$ reaction of 28 with 3.

Experimental Section

All photostimulated reactions were conducted in a Rayonet RPR-240 photochemical reactor[45] which possessed four 12.5 W bulbs emitting maximally at 350 nm. If the reaction solvent was liquid ammonia, the vacuum jacketed Pyrex vessel illustrated in Figure I was employed. The reactions in tetrahydrofuran (THF) were carried out in the Pyrex vessel illustrated in Figure II. Dark reactions were conducted in a darkened laboratory using standard Pyrex glassware enclosed in a black shroud.

Gas chromatographic (GC) analyses and separations were accomplished on Varian Associates 90-P or 1200 instruments using columns of 2% or 5% Carbowax 20M on Chromosorb G-HP and operating between 150 and 225°C. Acenaphthene or 4-methylquinoline were employed as internal standards[46] for the GC analyses. ^{1}H NMR spectra were determined on a JOEL JMN-PS-100 spectrometer at 100 MHz using tetramethylsilane as a reference. Mass spectra were determined by Jorge I. Bedia or Douglas S. Shearer on a Hitachi Perkin-Elmer-RMU 6E mass spectrometer. Infrared spectra were produced on a Beckman IR-20A-X spectrophotometer. Microanalyses were determined in this department by Jorge I. Bedia or Roger W. Stringham on a Perkin-Elmer 240 elemental analyzer. Melting points were observed in a Thomas-Hoover apparatus and are uncorrected.

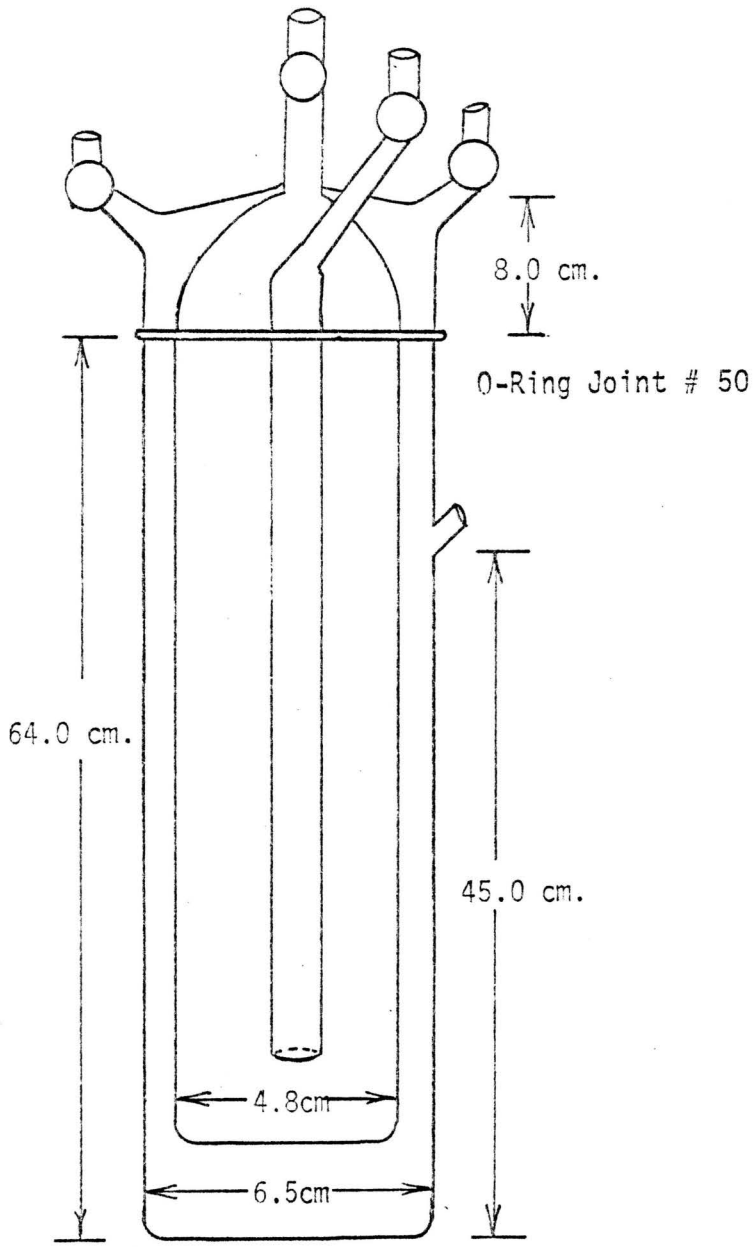
Tetrahydrofuran (THF) was refluxed over lithium aluminum hydride several hours prior to distillation and was stored in bottles under argon and over molecular sieves. 2-Bromopyridine was distilled from



LIQUID AMMONIA REACTION VESSEL

FIGURE I

DESIGN: Mark Sleevi
REALIZATION: Andrew Mollick



PHOTOLYSIS REACTION VESSEL

FIGURE II

DESIGN: Subrata Chatterjee
REALIZATION: Andrew Mollick

barium oxide and 2-chloroquinoline was fractionated at reduced pressure. 4-Picoline was fractionated, acetonitrile was distilled from P_2O_5, and both were stored in bottles over molecular sieves. 2-Aminoquinoline[23], 2-methylquinazoline[22], and 2-quinolylacetonitrile[25] were prepared as described elsewhere. 4-Bromopyridine hydrochloride and all other reagents were commercial grade and were used without further purification.

Photostimulated Reaction of 2-Chloroquinoline (9) with a 1:2 Ratio of Potassium Amide to Acetonitrile

This procedure serves as an example for conducting the experiments given in Table I.

Liquid ammonia (300 mL) was introduced into a reaction vessel (Figure I) containing a metal stirring bar and topped with a Dry Ice condenser. Nitrogen was forced through to keep moisture out as a catalytic amount of ferric nitrate and potassium metal (2.93 g; 75 mmol) were added. When the resulting blue solution turned grey, acetonitrile (6.16 g; 150 mmol) dissolved in ether was added to the stirred solution. After about 15 min the vessel was lowered into the illuminated photoreactor. A solution of 2-chloroquinoline (3.27 g; 20 mmol) dissolved in ether was added to the mixture. After 15 min the reaction was quenched by pouring the solution directly onto a slight excess of solid ammonium chloride contained in a beaker. As the ammonia evaporated THF was added to solubilize the mixture. Acenaphthene (200 mg; 1.3 mmol) was added as a GC standard. The resulting solution was filtered. The residue was washed with additional THF and filtered. The THF solutions were combined and concentrated. GC Analysis: 3-cyano-2-methyl-

quinoline (20) 1.09 mmol (5%); 2-quinolyl acetonitrile (11) 3.87 mmol (19%).

Preparative GC of the mixture afforded 20 as beige needles, mp 129-130°C. IR (KBr pellet)ν 2235 cm^{-1} (CN); mass spectrum m/e 168(M^+); ^1H NMR ($CDCl_3$)δ 2.91 (s,3H,CH_3), 7.43-8.03 (m, 4H, aromatic), and 8.38 (s, 1H, aromatic). In addition, 11 was isolated as a yellow oil (did not crystallize) IR (NaCl plates)ν 2240 cm^{-1} (CN); H NMR ($CDCl_3$)δ 4.03 (s, 2H, CH_2) and 7.40-8.04 (m, 6H, aromatic).

Photostimulated Reaction of 2-Chloroquinoline (9) and Potassioacetonitrile (5) in Liquid Ammonia

Liquid ammonia (300 mL) was introduced into a reaction vessel (Figure I) containing a metal stirring bar and topped with a Dry Ice condenser. Nitrogen was forced through to keep moisture out as a catalytic amount of ferric nitrate and potassium metal (2.93 g; 75 mmol) were added. When the resulting blue solution turned grey, acetonitrile (3.08 g; 75 mmol) dissolved in ether was added to the stirred solution. After 15 min the vessel was placed in the illuminated Rayonet photochemical reactor.[45] To the stirred solution was added 2-chloroquinoline (3.27 g; 20 mmol) dissolved in ether. The intensely orange solution was quenched after 15 min by pouring over NH_4Cl. The ammonia was allowed to evaporate. Acetone washes were combined and concentrated. After standing at room temperature for two weeks the solution was triturated with ether affording two major "polymer" fractions, one of 0.58 g (mp 140-185°C) and the other of 0.95 g (mp 114-120°C). The remaining organic solution was concentrated and treated with ethanol. Crude 3-methyl-2-

(2'-quinolyl)-2-butenonitrile (17) precipitated. Recrystallization from ethanol afforded bright yellow needles of 17 0.53 g (16%) mp 100-101.5°C. IR ($CHCl_3$)ν 2220 cm^{-1} (CN); ^1H NMR ($CDCl_3$)δ 2.20 (s,3H,CH_3), 2.34 (s, 3H,CH_3), and 7.44-8.20 (m,6H, aromatic); mass spectrum m/e 208 M^+; Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.26; H, 5.75; N. 13,40. Preparative GC of the remaining solution afforded various mixtures of 11, 21, 17 and 20 as determined by ^1H NMR.

Photostimulated Reaction of 9 and 5 in THF

A 22% suspension of potassium hydride in mineral oil (9.11 g; 50 mmol) was washed with hexane and transferred to the reaction vessel shown in Figure II. After the solid had settled the hexane was decanted and replaced with dry THF. The stirred solution was kept under a positive pressure of nitrogen as acetonitrile (2.05 g; 50 mmol) dissolved in THF was added to the vessel. Anion formation was allowed for 20 min before irradiation was begun. 2-Chloroquinoline (9) (1.64 g; 10 mmol) dissolved in THF was added and the resulting dark red solution was quenched with water after 1 hr. Acenaphthene (118.9 mg; 0.77 mmol) was added as a GC standard. The aqueous layer was removed and extracted several times with ether. These extracts were combined with the THF layer, dried with $MgSO_4$, filtered and concentrated. GC analysis: 2-chloroquinoline (9) 36%, 3-cyano-2-methylquinoline (20) 9% and 2-quinolylacetonitrile (11) 31%. All of the products' spectral characteristics agreed well with those of authentic samples.

A 2 h irradiation using 20 mmol of 9 was done. Chromatography on silica gel with the eluent, methylene chloride, afforded, in addition to

other products which were not quantitated, 0.65 g (22%) of α-2-quinolinyl-2-quinolineacetonitrile (18 (19)) as a feathery orange solid, mp 280-282°C (lit[47] mp 281-283°C). IR (KBr)ν 2200 cm^{-1} (CN); ^1H NMR ($CDCl_3$) δ 7.26-8.12 (multiplet, aromatic); mass spectrum m/e 295 (M^+), 147.5 (M^{++}). Anal. Calcd. for $C_{20}H_{13}N_3$: C, 81.34; H, 4.43; N, 14.23. Found: C, 81.11; H, 4.81; N, 14.11.

Attempted Methylation of α-2-Quinolinyl-2-quinolineacetonitrile (18)

In a round-bottomed flask fitted with a condenser was placed 18 (0.148 g; 0.5 mmol) and 50 mL of THF. The mixture was heated until the solid was solubilized whereupon methyl iodide (0.072 g; 0.5 mmol) was added. No change was observed after refluxing the solution for 30 min. Triethylamine (0.051 g; 0.5 mmol) was added to the refluxing solution with no noticeable effect after 1 h. Additional portions of methyl iodide and triethylamine were added. After 4 h from the initial addition of methyl iodide a white precipitate was observed. The reaction was assumed complete after another hour since the amount of precipitate did not increase. The mixture was cooled, quenched with water, and saturated with salt. The organic layer was combined with the ether extracts of the aqueous layer. These were dried with $MgSO_4$ and concentrated under vacuum. An orange solid formed which was thought to be 18, 0.11 g (74%). ^1H NMR of this solid showed no methyl signal and was identical to that of 18. A modification of this procedure using NaH instead of triethylamine as a base failed to yield the desired compound.

Synthesis of 3-Cyano-2-Methylquinoline (20)

An adaptation of E. A. Fehnel's procedure was followed.[33] Freshly prepared cyanoacetone[48] (1.66 g; 20 mmol) and o-aminobenzaldehyde[49] (2.42 g; 20 mmol) were placed into a 3-necked round-bottomed flask fitted with a condenser. Glacial acetic acid (20 mL) was immediately added to the mixture. The stirred mixture was heated for about 3 min after which 0.2 mL of 18 M sulfuric acid was added. The resulting maroon solution was refluxed for 3 h and was quenched by adding the solution to a cold solution of 30 mL of 15 M ammonium hydroxide and 60 mL of water. The crude solid which formed was filtered and recrystallized from aqueous ethanol affording 2.07 g (62%) of bright yellow needles, (20), mp 132-133.5°C. IR (KBr pellet)ν 2230 cm^{-1} (CN), mass spectrum (m/e) 168 (M^+), ^1H NMR ($CDCl_3$)δ 2.93 (s,3H,CH_3), 7.49-8.07 (m,4H, aromatic), 8.42 (s,1H, aromatic). Anal. Calcd. for $C_{11}H_8N_2$: C, 78.56; H, 4.79; N, 16.34. Found: C, 78.27; H, 4.55; N, 16.34.

Bromination of Quinaldine with Bromine in Dichloromethane

An adaptation of Mathes' and Schuly's methods[24] was used. In a 3-necked flask fitted with a condenser was added quinaldine (14.9 g, 100 mmol) dissolved in 150 mL of dichloromethane. To the solution was added Na_2CO_3 (10.6 g; 100 mmol) and a few crystals of dibenzoyl peroxide. Slowly, Br_2 (16 g; 100 mmol) dissolved in dichloromethane was added dropwise. The mixture warmed to a boil and was refluxed for 24 h after all of the bromine solution was added. The resulting mixture was neutralized with dilute HCl. The organic layer was extracted with 3 N HCl solution. The latter aqueous solution was neutralized and extracted with

dichloromethane. The last organic layers were combined, dried, concentrated, and distilled to afford quinaldine 4.6 g (31%). The first mentioned dichloromethane solution was concentrated and taken up in ethanol. Crude α,α-dibromoquinaldine (15) 4.9 g (16%) mp 91-110°C was isolated. Several recrystallizations from ethanol afforded 1.8 g (6%) of 15, mp 121-122°C (lit[50] mp 117-120°C). ^{1}H NMR ($CDCl_3$)δ 6.25 (s,1H,CH) and 7.6-8.5 (m,6H, aromatic). Anal. Calcd. for $C_{10}H_7NBr_2$: C, 39.91; H, 2.35; N, 4.65; Br, 53.09. Found: C, 39.79; H, 2.06; N, 4.15; Br, 53.53. Their chlorination procedure was also tried without success.

Bromination of Quinaldine with N-Bromosuccinimide in Benzene

An adaptation of Ottermann's and Vogtle's procedure[25] was followed. Quinaldine (5 g; 34.9 mmol) was weighed into a 2-necked flask, fitted with a condenser. Approximately 60 mL of benzene, N-bromosuccinimide (6.4 g; 36 mmol) and few crystals of azobis-(isobutyronitrile) were added to the flask. The mixture was stirred at reflux under N_2 for 21 h with illumination from a 150 W flood lamp. The resulting solution was washed with aqueous NH_4OH and water and finally was filtered. The filtrate was dissolved in chloroform, and treated with charcoal, and extracted several times with petroleum ether. These extracts were concentrated and the dark globules that settled to the borrom were removed. After cooling overnight, crude yellowish crystals, mp 45-65°C, which quickly turned grey in air, were isolated. Analysis by ^{1}H NMR showed them to be a mixture of α-bromoquinaldine (∿60%) and α,α-dibromoquinaldine (∿40%). Changing the solvent from benzene to carbon tetrachloride failed to improve the results of the reactions.

Attempted Preparation of 2-Quinolylacetonitrile (11) from Cyanogen Bromide and α-Lithioquinaldine

In a 3-necked round-bottomed flask equipped with a teflon-coated magnetic stirring bar was placed approximately 100 mL of dry THF and quinaldine (14.3 g; 0.1 mol). The mixture was kept under an atmosphere of nitrogen as it was cooled in a Dry Ice-alcohol bath. A 1.4 M solution of butyllithium in hexane (70 mL; 0.1 mol) was added to generate the intense maroon anion. This anion solution was added to a cooled THF solution of cyanogen bromide[51] (18 g; 0.17 mol) and the yellow suspension formed was stirred for 20 min before it was allowed to come to room temperature. On concentrating and standing crude 1,2-di(2'-quinolyl) ethane (16) 8.48 g (60%) precipitated. Recrystallization several times from methanol afforded faintly beige needles, mp 165-166°C (lit[52] mp 166-167°C). ^{1}H NMR ($CDCl_3$)δ 3.56 (s,4H,CH_2) and 7.30-8.12 (m,12H, aromatic). Anal. Calcd. for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.31; H, 5.52; N, 9.96.

Photostimulated Reaction of 2-Bromopyridine (1) and Potassio-4-picoline (3)

This procedure serves as an example for conducting the experiments given in Table II.

In a cylindrical reaction vessel (see Figure I), fitted with a Dry Ice condenser and a nitrogen bubbler, was placed a few crystals of ferric nitrate nonahydrate and 300 mL of liquid ammonia. Potassium metal (2.93 g; 75 mmol) was added and the blue solution was allowed to stir until it became grey, indicating amide formation. 4-Picoline (6.98 g,

75 mmol) was added and the blue solution was allowed to stir until it became grey, indicating amide formation. 4-Picoline (6.98 g, 75 mmol) dissolved in ether was added to the solution. The vessel was placed in the photolysis chamber and after 20 min, 2-bromopyridine (3.16 g; 20 mmol) mixed with ether was added to the solution. The mixture was irradiated for 15 min and quenched by pouring the solution onto ammonium chloride. The ammonia was boiled off and replaced with ether. 4-Methylquinoline (0.425 g; 2.97 mmol) was added as an internal standard for GC analysis. The resulting solution was filtered, concentrated and analyzed by gas chromatography. Results: 2,4-dipyridylmethane (4) 7.35 mmol (37%) and 2-aminopyridine (2) 10.64 mmol (53%). Isolation of hygroscopic 4 by preparative GC afforded a colorless oil. ^{1}H NMR δ 4.09 (s, 2H,CH_2), 7.01-7.16 (m,4H,aromatic), 7.40-7.62 (m,1H,aromatic) and 8.32-8.52 (m,3H,aromatic). Microanalyses for this compound were unsatisfactory because of its hydroscopic nature.

Photostimulated Reaction of 4-Bromopyridinium Hydrochloride (28) and Potassio-4-picoline (3)

In a cylindrical reaction vessel (see Figure I), fitted with a Dry Ice condenser and a nitrogen bubbler, was placed a few crystals of ferric nitrate nonahydrate and 300 mL of liquid ammonia. Potassium metal (3.91 g; 100 mmol) was added and the blue solution was allowed to stir until it became grey, indicating amide formation. 4-Picoline (9.31 g, 100 mmol) dissolved in ether was added to the solution. The vessel was placed in the photolysis chamber and after 20 min, 4-bromopyridinium hydrochloride (28) (3.89 g; 20 mmol) was added as a solid as quickly as

possible. The solid adhering to the vessel walls was washed in with ether. The mixture was irradiated for 15 min and quenched by pouring the solution onto ammonium chloride. The ammonia was boiled off and replaced with ether and THF. Acenaphthene (0.371 g; 2.4 mmol) was added as internal standard for GC analysis. The resulting solution was filtered, concentrated and analyzed. Results: 4,4'-dipyridylmethane (29) 15.53 mmol (78%), 4-aminopyridine (30) < 1%, and 1,2-di(4-pyridyl)-ethane 6%. Isolation of hygroscopic 29 by preparative GC afforded a pale yellow oil which solidified only on cooling. ^{1}H NMR δ 3.95 (s,2H,CH_2), 7.09 (m,4H,aromatic), and 8.55 (m,4H, aromatic). Microanalyses for this compound were unsatisfactory because of its hydroscopic nature.

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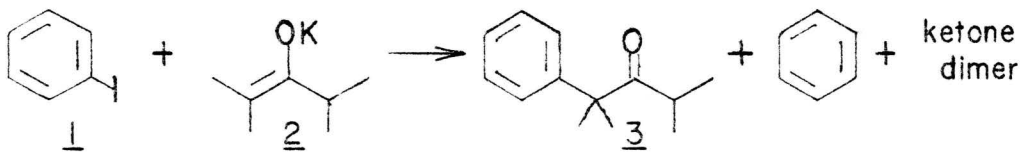
CHAPTER IV[1]

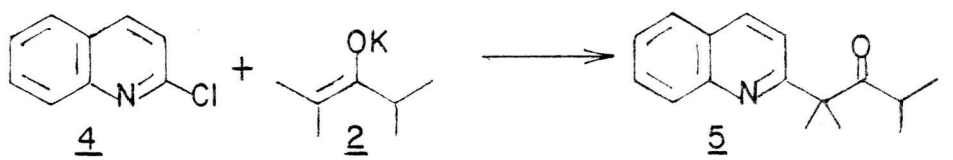
Synopsis: A brief study on the formation of ketone dimers resulting from a hydrogen atom transfer side reaction which competes with $S_{RN}1$ reactions.

During their investigation of photostimulated arylations of ketone enolates by the $S_{RN}1$ mechanism, Bunnett and Sundberg[2] reported the sluggish reaction of iodobenzene (1) with potassio-2,4-dimethylpentanone (2) in liquid ammonia (equation 1). In addition to the expected 2,4-dimeth-



1 2 3 (1)

yl-2-phenyl-3-pentanone (3), obtained in 32% yield, there was observed benzene (19%), a ketone dimer (20%), and unreacted 1 (48%) after three hours of irradiation. In contrast, Wolfe and coworkers[3,4] have found that the photostimulated reaction of anion 2 with 2-chloroquinoline (4) and 2-bromopyridine (6) in liquid ammonia afforded, as shown in equations 2 and 3, the arylated ketones 5 and 7 in 94% and 97% yields,



4 2 5 (2)

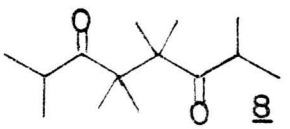
6 2 7 (3)

respectively, after only one hour. There was also observed 5% of a

ketone dimer from the reaction of equation 3 which was identical to that obtained from the reaction of 1 with 2.

Discussion and Results

The structure initially proposed for the ketone dimer produced in these reactions was that of compound 8. However, upon re-examining the



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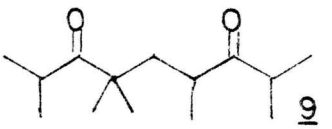
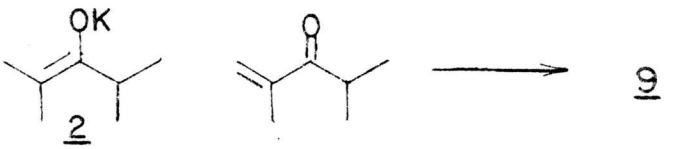


9

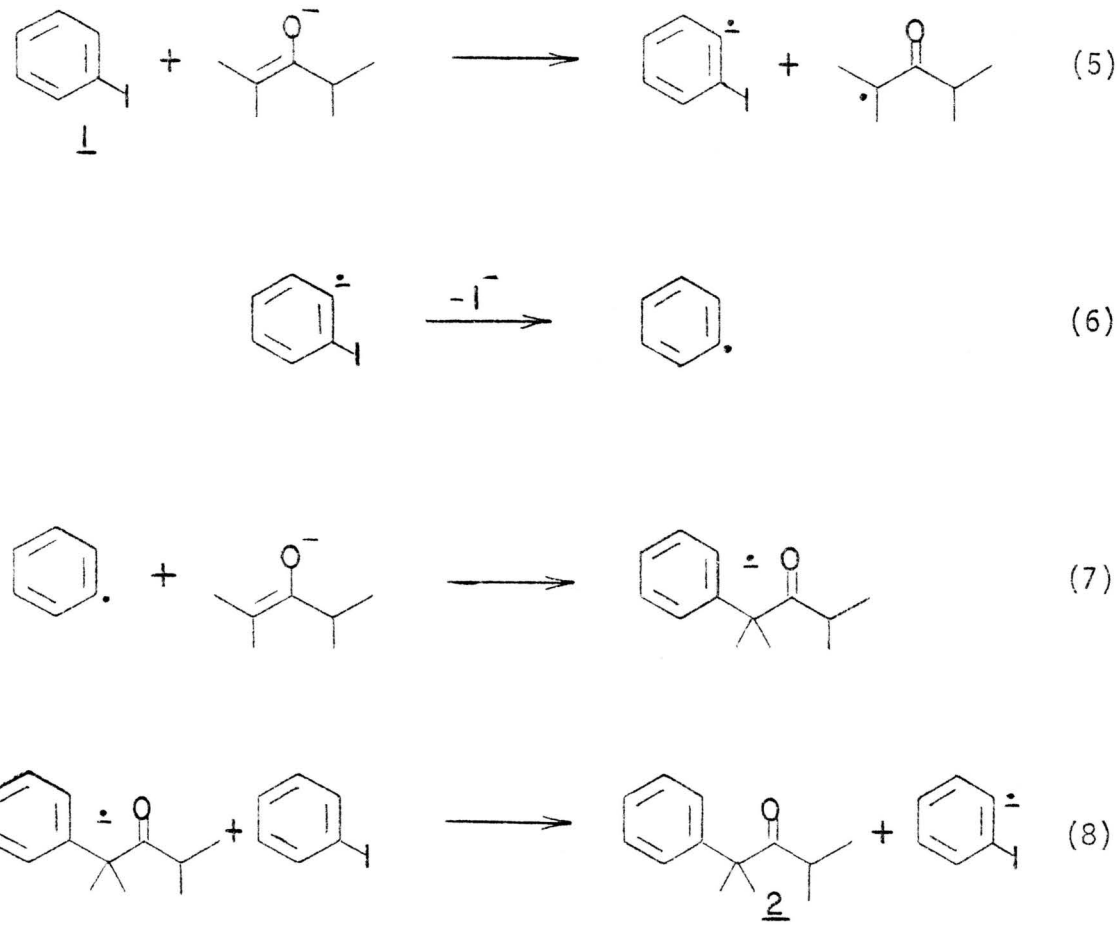
spectral data for this compound more critically, it was determined that the ketone dimer was actually 9 instead of 8.[5] Because of its symmetrical nature, the ^{1}H NMR spectrum of 8 should be less complex than that of 9, whose diastereotopic methylene hydrogens and adjacent methine hydrogen would give rise to an ABX spin system. In addition, the ^{13}C NMR spectrum of 8 shows only one carbonyl resonance, whereas that of 9 shows two. That 9 was the correct structure was further substantiated by comparing the spectrum of 9 obtained from the Michael addition of 2 to 2,4-dimethyl-1-penten-3-one (equation 4) with that of 9 isolated from the reaction of 1 with 2.



2 9 (4)

The proposed[6] mechanism for $S_{RN}1$ reactions is given in Scheme I. Chain initiation is depicted in equation 5 and is postulated to involve an electron transfer from the nucleophile, 2, to 1 generating its radical anion. In the three ensuing propagation steps, this radical anion

SCHEME I

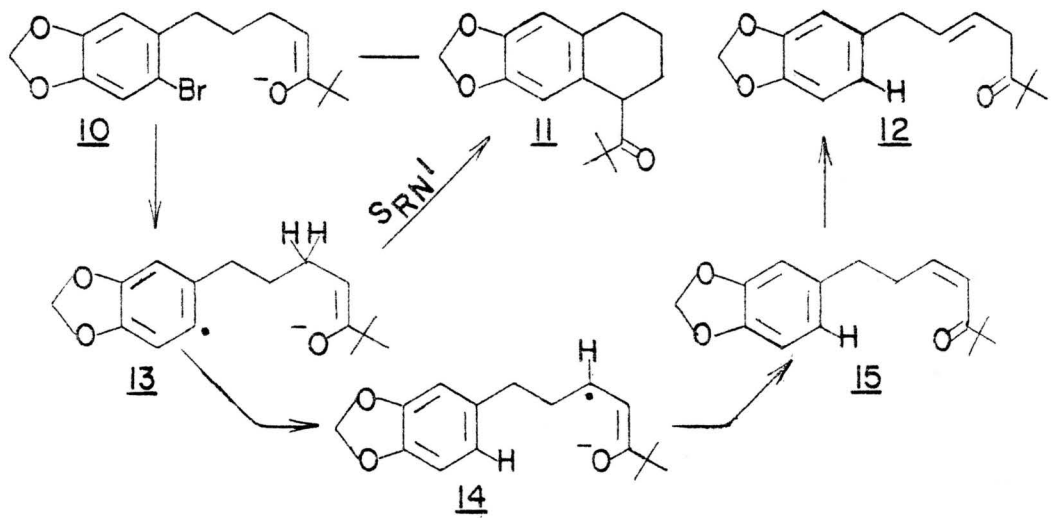


expels iodide ion, as shown in equation 6, leaving the aromatic radical available for attack by 2 (equation 7) and thus producing the product radical anion which may transfer an electron, as in equation 8, to unreacted 1. Nevertheless, this mechanism alone does not account for the formation of 9.

The formation of 9 may be explained in terms of a hydrogen atom abstraction pathway first delineated by Semmelhack and Barger[7] during their study of intramolecular photostimulated $S_{RN}1$ reactions. They found that in some ring closure reactions of certain methylenedioxophenyl

derivatives with ketone side chains, a competing side reaction involving the reductive dehalogenation of the aromatic ring and subsequent formation of an unsaturated ketone moiety, such as in 12 (Scheme II), occurred. The suggested pathway shown in Scheme II involves electron

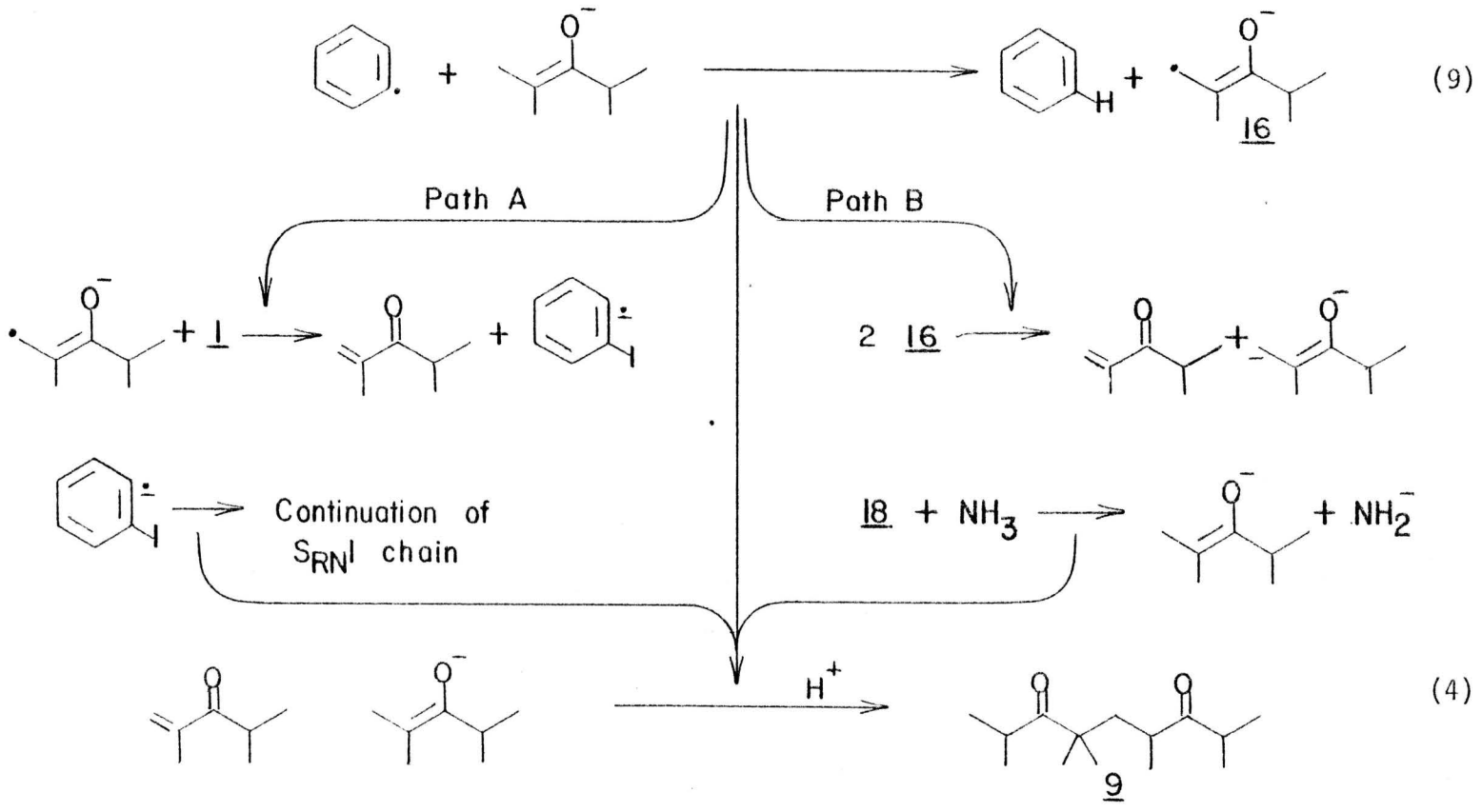
SCHEME II



transfer to the aromatic portion with subsequent loss of bromide ion to form 13, which corresponds to the $S_{RN}1$ mechanism steps given in equations 5 and 6 of Scheme I. In these systems, it is apparently more favorable for the resulting aryl radical to abstract a β-hydrogen to form 14 rather than ring close to 11 via the $S_{RN}1$ pathway. Radical anion 14 would then transfer an electron to a suitable acceptor and thus form 15, which, in this example, rearranges to 12.

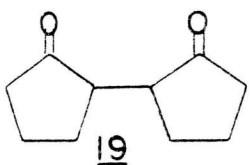
In an analogous manner, one can envision the reaction of 1 and 2 to involve a hydrogen abstraction step (equation 9) as shown in Scheme III. The resulting enone, 17, is susceptible to nucleophilic attack by the

SCHEME III

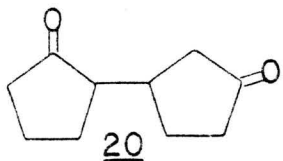


excess 2 in solution to ultimately form 9. Two different pathways are offered for the formation of enone 17 (Scheme III). Path A illustrates the chain continuing transfer of an electron from radical anion 16 to 1 to form 17. Path B illustrates the chain terminating disproportionation of 16 to 17 and dianion 18 which would be rapidly protonated by the solvent. If the production of dimer 9 followed Path A, then the rate of reaction should be enhanced because of the additional source available for initiating these radical chain reactions. However, the rate of reaction for 1 with 2 is slow and is more conveniently explained by Path B, whose chain terminating steps could very well impede the reaction's progress.

Other ketones with β-hydrogens would be expected to give products analogous to 9. Nevertheless, the photostimulated reaction of cyclopentanone anion with bromobenzene was reported to afford, in addition to other products, dicyclopentyl-2,2'-dione (19) instead of the unsymmetrical diketone 20.[2] Thus attempts were made to resolve this problem.

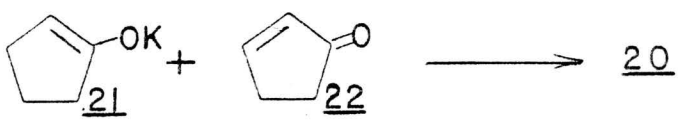


19



20

The synthesis of dimer 20 should logically be accomplished in the same manner as was the synthesis of 9. Equation 10 illustrates the



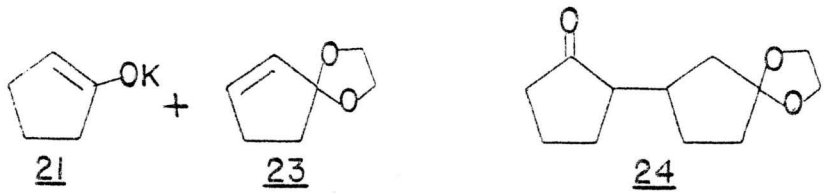
21 + 22 ⟶ 20 (10)

desired Michael addition of potassiocyclopentanone (21) to 2-cyclo-

penten-1-one (22). However, attempts to realize this addition were unsuccessful. The only characterizable product obtained from the attempted Michael addition was a solid believed to be some sort of polymer. This material displayed broad ^{1}H and ^{13}C NMR resonances and had a melting point range of 145-160°C, which is close to the second order transition temperature of 150°C reported by Longi and coworkers[8] for their polymers of 22. These authors reported anion polymerizations of 22 and other enone systems in toluene which were promoted by several bases, such as lithium diethyl amide, sodium amide, potassium diphenyl amide, and phenyl magnesium bromide. After 24 hours, only a 40% conversion to polymer was observed in toluene at 0°C, but this reaction time would be expected to drop sharply in a more polar solvent, such as liquid ammonia, in which anion reaction rates are usually enhanced.

The failure of the Michael reaction of 21 and 23 to afford an observable amount of 20 does not eliminate the possibility that this compound may be formed in the $S_{RN}1$ reaction of bromobenzene with 21. Polymerization could be the favored process when large amounts of enone 22 are present. If the enone reacts as it is formed, then no appreciable concentration of 22 would be present at any time for self-condensation.

Assuming that the problem with this condensation lay in the extreme reactivity of the enone, another Michael type addition was attempted on the ethylene ketal of 22 (23) as shown in equation 11. Instead of the desired product (24), there was only observed the starting materials 21 and 23 from this attempted reaction. The failure of this reaction may be attributed to either the unreactivity of ketal 23, or to the

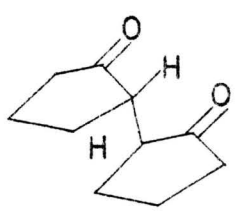


21 23 24 (11)

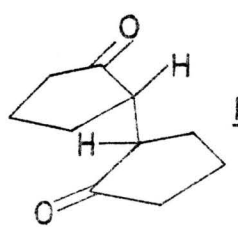
reversibility of the addition of 21 to 23.

The symmetrical ketone dimer 19 was synthesized by an oxidative coupling reaction using cupric chloride.[9] The ^{1}H NMR spectrum of this compound was compared to that of the major "ketone dimer" fraction isolated from the reaction of bromobenzene and 21. They were observed to be different, but, due to their complex spectra, it was difficult to conclude that the isolated dimer was really 20.

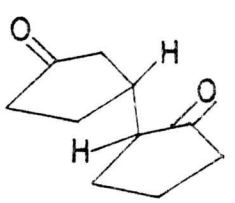
The ^{13}C NMR spectra of these two compounds were determined. The spectrum of the symmetrical ketone dimer 19 contained two carbonyl carbon resonances which result from the two diastereomers, 19a and 19b



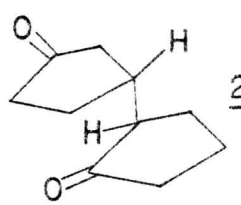
19a



19b

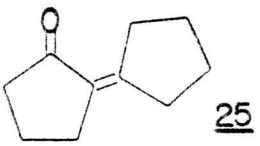


20a



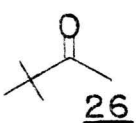
20b

shown above, of 19. In each diastereomer of 19 the carbonyl carbons are equivalent; however, those of 20 are nonequivalent. Thus, there should be four carbonyl carbon resonances observed for the diastereomers 20a and 20b. The ^{13}C NMR of the isolated "ketone dimer" possessed only one carbonyl carbon resonance. The presence of two alkene carbon resonances suggests that the isolated compound was 2-cyclopentylidenecyclopentanone (25) rather than 20.

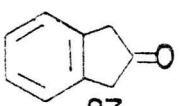


25

Ketone dimers produced in these reactions are not limited to those obtained by the hydrogen atom transfer pathway. There have been observed dimers of pinacolone (26)[4] and 2-indanone (27),[2] neither of which



26



27

can form an enone such as 17 and thus, must couple by some other pathway. The dimerization of 26 has been reported to be stimulated by light and possibly involves radical coupling.[4]

Conclusions

One may conclude that the hydrogen atom abstraction side reaction inhibits the $S_{RN}1$ reaction of substrates with enolates having β-hydrogens. The mechanism shown in Scheme III (Path B) is offered as an explanation for the sluggishness of the reactions observed with the halobenzenes. The ineffectiveness of this side reaction in significantly retarding the

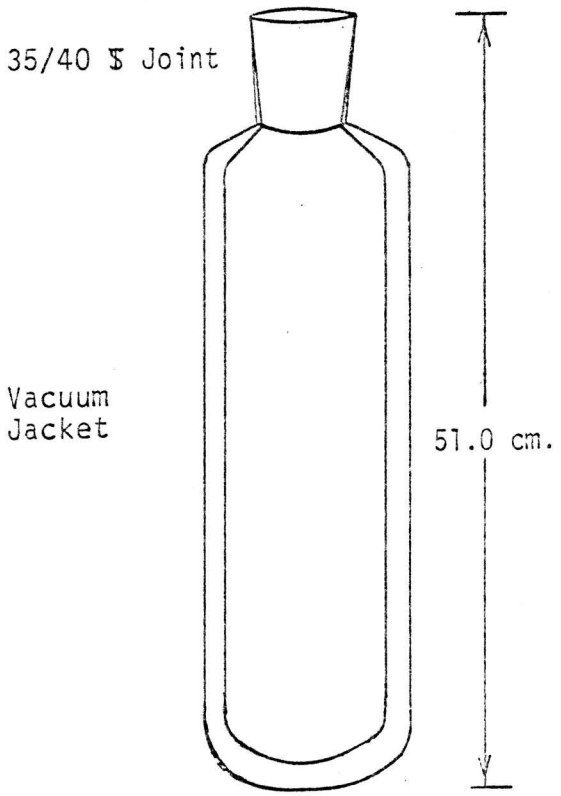
$S_{RN}1$ reactions of the heteroaromatic halides can be attributed to the greater reactivity of the heterocycles.[4] Possibly radical coupling can account for dimers that are formed in reactions with other ketones.

Experimental Section

The photostimulated reactions were conducted in a Rayonet RPR-240 photochemical reactor[10] which possessed four 12.5 W bulbs emitting maximally at 350 nm and employed the pyrex vessel illustrated in Figure I. All other reactions were performed using standard Pyrex laboratory glassware.

Gas chromatographic (GC) separations were accomplished on a Varian Associates 90-P instrument using a column of 2% Carbowax 20M on Chromosorb G-HP and operating between 150-200°C. ^1H NMR were determined on a JEOL JMN-PS-100 spectrometer at 100 MHz using tetramethylsilane as a reference. ^{13}C NMR were determined by T. E. Glass on a similar instrument equipped with a Digilab FTS-NMR Data System at 25.15 MHz using tetramethylsilane as a reference. Infrared spectra were produced on a Beckman IR 20-A-X spectrophotometer. Microanalyses were determined either by Jorge T. Bedia, at this institution, on a Perkin-Elmer 240 elemental analyzer, or by Galbraith Laboratories, Knoxville, Tennessee. Melting points were observed in a Thomas-Hoover apparatus and are uncorrected as are the boiling points.

2,4-Dimethyl-1-penten-3-one (17),[11] 2,4,4,5,5,7-hexamethyl-3,6-octanedione (8),[12] and 2-cyclopenten-1-one ethylene ketal (23)[13] were prepared as in the superscripted references. Commercially available 2-cyclopenten-1-one, cyclopentanone, 2,4-dimethyl-3-pentanone, and all



LIQUID AMMONIA REACTION VESSEL

FIGURE I
DESIGN: Mark Sleevi
REALIZATION: Andrew Mollick

other reagents were used without further purification.

Michael Addition of Potassio-2,4-dimethyl-3-pentanone (2) to 2,4-Dimethyl-1-penten-3-one (17)

Liquid ammonia (100 mL) was introduced into a round-bottomed flask fitted with a Dry Ice-alcohol condenser. A few crystals of ferric nitrate was added. The system was kept under an atmosphere of nitrogen as potassium metal (0.82 g; 21 mmol) was added. After the blue color of the solution discharged, 2,4-dimethyl-3-pentanone (2.40 g; 20 mmol) dissolved in ether was added and after 20 min the anion was assumed formed. The enone, 17[11] (2.24 g; 20 mmol) dissolved in ether was added. After 1 h the greenish solution was quenched by pouring the reaction mixture onto ammonium chloride. The ammonia was allowed to evaporate and the residue was washed with several portions of ether. These extracts were combined, concentrated, and fractionated through a 4 cm helices packed column to afford 2.95 g (65%) of a faintly pale yellow oil, 9, bp 68-70°C at 0.24 mm. IR (neat)ν 1705 cm^{-1} (C=O). ^1H NMR ($CDCl_3$)δ 1.10 (m, 21H, CH_3), 1.42 (d of d, 1H, CH_2), 2.15 (d of d, 1H, CH_2), 2.56 (m, 1H, CH), 2.67 (sept, 1H, CH), 3.07 (sept, 1H, CH). ^{13}C NMR ($CDCl_3$)δ 18.7, 18.9, 19.9, 20.1, 20.3, 23.7, 25.3, 34.1, 39.8, 41.2, 41.4, and 48.3 (s, 1C, saturated carbon), 217.4 and 219.3 (s, 1C, carbonyl carbon). Anal. Calcd. for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58. Found: C, 74.45; H, 11.63.

Photostimulated Reaction of 2 with Iodobenzene (1)

Liquid ammonia (300 mL) was introduced into a Pyrex reaction vessel (Figure I) fitted with a dry ice-alcohol condenser and an inlet for

nitrogen. A catalytic amount of ferric nitrate was added. After the addition of potassium metal (2.93 g; 75 mmol) amide formation was observed after about 30 min. 2,4-Dimethyl-3-pentanone (7.55 g; 75 mmol) dissolved in ether was added to the mixture, and after 15 min the anion was assumed formed. The reaction vessel was lowered into the illuminated photoreactor, whereupon iodobenzene (4.08 g; 20 mmol) was added. The solution was quenched after 3 h by pouring the solution over ammonium chloride. The ammonia was allowed to evaporate and the residue was washed several times with ether. The extracts were filtered, combined, and concentrated. Preparative GC of the reaction mixture afforded, in addition to 2,4-dimethyl-2-phenyl-3-pentanone, an oil with IR spectra and ^{1}H and ^{13}C NMR spectra which were identical to that of the independently synthesized 9.

Photostimulated Reaction of Potassiocyclopentanone (21) with Bromobenzene

Liquid ammonia (300 mL) was added to a Pyrex reaction vessel (Figure I) which was fitted with a Dry Ice-alcohol condenser and an inlet for nitrogen. A catalytic amount of ferric nitrate was added and was followed by potassium metal (2.93 g; 75 mmol). Amide formation was complete after 30 min. Cyclopentanone (6.31 g; 75 mmol) dissolved in ether was added to the mixture and after 15 min a grey suspension of 21 was observed. The vessel was lowered into the illuminated photoreactor after which bromobenzene (3.1 g; 20 mmol) dissolved in ether was added. The solution was quenched after 3 h by pouring the solution over ammonium chloride. The ammonia was allowed to evaporate and the residue was washed several times with ether. The extracts were filtered, combined,

concentrated. Preparative GC afforded, in addition to several minor products, 2-phenylcyclopentanone as a pale yellow oil; ^{1}H NMR ($CDCl_3$)δ 1.80-2.90 (m, 7H, aliphatic H), 7.11-8.04 (m, 5H, aromatic H) and 2-cyclopentylidenecyclopentanone (25) as a pale yellow oil; IR (neat)ν 1645 cm^{-1} (C=C), 1725 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$)δ 1.60-2.90 (m, aliphatic H); ^{13}C NMR ($CDCl_3$)δ 20.1, 25.2, 27.0, 29.5, 32.6, 34.3, and 39.8 (s, aliphatic C), 127.9, 158.6 (s, alkene C), and 207.3 (s, carbonyl C).

Attempted Michael Reaction of 21 with 2-Cyclopenten-1-one (22)

Liquid ammonia (100 mL) was added to a round-bottomed flask fitted with a Dry Ice-alcohol condenser. A few crystals of ferric nitrate were added. The system was kept under an atmosphere of nitrogen as potassium metal (1.06 g; 27 mmol) dissolved in ether was added. After the formation of potassium amide was observed, cyclopentanone (2.27 g; 27 mmol) dissolved in ether was added and after about 20 min the anion was assumed formed. To this solution was added 22 (2.05 g; 25 mmol) dissolved in ether. After 1 h the mixture was quenched by pouring onto ammonium chloride. The ammonia was allowed to evaporate and the residue was washed with ether and tetrahydrofuran. The extracts were filtered and concentrated. Trituration of this mixture with ether afforded 1.17 g of a beige solid thought to be polymer. IR (KBr)ν 3440 cm^{-1} (OH), 1730 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$)δ 2.0-4.0 (broad resonance); ^{13}C NMR ($CDCl_3$)δ 20.0-55.0 (broad aliphatic resonances), and 213-223 (broad carbonyl resonances).

Attempted Michael Addition of 21 to the Ethylene Ketal of 22 (23)

Liquid ammonia (100 mL) was added to a round-bottomed flask fitted

with a Dry Ice-alcohol condenser. A few crystals of ferric nitrate were added. The system was kept under an atmosphere of nitrogen as potassium metal (0.82 g; 21 mmol) was added. After the blue color of the solution discharged, cyclopentanone (1.77 g; 21 mmol) in ether was added dropwise. The thick grey suspension was stirred for about 15 min to insure anion formation. The ketal (23)[13] (2.52 g; 20 mmol) dissolved in ether was added to the mixture which gradually became quite thick. The reaction was quenched by pouring the solution over ammonium chloride. The ammonia was allowed to evaporate and the dregs were washed with ether, combined, filtered, and concentrated. The ^{1}H NMR spectrum of the crude reaction mixture showed only ether, cyclopentanone, and 23.

Preparation of (1,1'-Bicyclopentyl)-2,2'-dione (19)

An adaptation of the procedure of Saegusa and coworkers[9] was followed. In a round-bottomed flask immersed in a Dry Ice-alcohol bath was added a solution of diisopropyl amine (5.06 g; 50 mmol) in 50 mL THF. A 2.1 M solution of n-butyllithium in hexane (23.8 mL; 50 mmol) was added slowly to the solution so as to keep the reaction temperature low. After 15 min cyclopentanone (3.78 g; 45 mmol) dissolved in THF was added slowly to the solution. Anhydrous $CuCl_2$ (6.72 g; 50 mmol) dissolved in 60 mL of dimethyl formamide. The resulting brown solution turned green on cooling to -78°C. After 15 min, the cold green solution was added quickly to the THF solution. The resulting purple solution was stirred for 30 min at -78°C and then was allowed to reach room temperature. The reaction mixture was treated with 3% HCl and extracted with ether. The ether extracts were washed with 3% HCl and finally with

water before being dried over $MgSO_4$. The resulting purple mud was chromatographed on silica gel eluting with CCl_4 and finally with CH_2Cl_2 affording 0.5 g (13%) of a yellow oil, 19. IR (neat)ν 1745 (C=O), ^1H NMR ($CDCl_3$)δ 1.50-2.70 (m, aliphatic H), ^{13}C NMR ($CDCl_3$)δ 20.7, 20.9, 25.4, 26.8, 37.9, 38.1, 48.5, and 49.3 (s, aliphatic C) and 218.9 and 219.9 (s, carbonyl C).

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1. The presented work was done in collaboration with Mr. Mark C. Sleevi.

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THE EFFECTS OF SOLVENTS AND NUCLEOPHILES ON HETEROAROMATIC $S_{RN}1$ REACTIONS

by

Marcus P. Moon

(ABSTRACT)

This dissertation is concerned with three aspects of the nucleophilic substitution reactions of some heteroaromatic halides.

First, the $S_{RN}1$ reaction of 2-chloroquinoline with potassioacetone was studied in several solvents. Tetrahydrofuran (THF), dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and dimethoxyethane (DME) were found to be more suitable as solvents for this reaction than were diethylether and benzene. This reaction was stimulated by near UV irradiation. However, substantial reaction occurred in the more polar solvents without photostimulation. The $S_{RN}1$ character of these reactions was substantiated by inhibition studies. The relative rates of this reaction in the solvents generally increased with increased solvent polarity. The $S_{RN}1$ reactions of 2-chloroquinoline, 2-bromopyridine, and iodobenzene with ketone enolates in THF were found to occur slower than their analogous reactions in liquid ammonia.

Second, 4-picoline and acetonitrile anions were employed as nucleophiles for heteroaromatic $S_{RN}1$ reactions. The photostimulated reaction of 2-chloroquinoline with potassioacetonitrile in liquid ammonia was complicated by "polymer" formation and by S_NAr2 and S_N(ANRORC) reactions with equilibrium concentrations of potassium amide. In the absence of

photostimulation, 3-cyano-2-methylquinoline was the major product observed and presumably resulted from an interesting S_N(ANRORC) reaction involving potassioacetonitrile. Attempts to eliminate the side reactions with amide by employing excess acetonitrile resulted in increased yields of "polymer." The reaction of 4-picoline with 2-bromopyridine was also plagued with a significant competing amination reaction. However, moderate increases in the ratio of 4-picoline to potassium amide employed reduced the yields of 2-aminopyridine. In contrast, the $S_{RN}1$ reaction of 4-bromopyridine with potassio-4-picoline was accompanied by only trace amounts of 4-aminopyridine.

Lastly, the $S_{RN}1$ reactions of 2,4-dimethyl-3-pentanone with 2-bromopyridine and iodobenzene were accompanied by a reductive dehalogenation process. That these reactions involved the abstraction of β-hydrogens from the nucleophile was supported by the isolation of 2,4,4,5,5,7-hexamethyloctane-3,6-dione. Spectral characterizations and the independent synthesis of this ketone dimer is described. The search for a similar ketone dimer from the reaction of potassiocyclopentanone with bromobenzene was inconclusive.