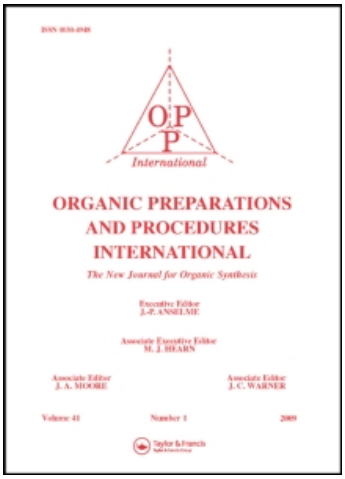

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THE $S_{RN}1$ REACTION IN ORGANIC SYNTHESIS. A REVIEW

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THE $S_{RN}1$ REACTION IN ORGANIC SYNTHESIS. A REVIEW

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I. INTRODUCTION

Aromatic nucleophilic substitution, as generalized in eq. 1 for an aromatic substrate reacting with nucleophile :Y, has long been a subject of interest in organic chemistry.

$$Ar\text{-}X + :Y \longrightarrow Ar\text{-}Y + :X \qquad (1)$$

Such reactions have been studied more often for their fascinating mechanistic features than for their synthetic utility, and the interested reader may find several excellent reviews dealing with this topic.[1-4]

One of the reasons that aromatic nucleophilic substitutions have not previously challenged the synthetic prominence of electrophilic aromatic substitutions lies in repeated observations that displacement of potential leaving (nucleofugic)[5] groups from an aromatic nucleus requires rather stringent reaction conditions unless the substrate is activated by electron-withdrawing substituents in conjuction with a suitable nucleofugic group. Although unactivated aryl halides will react with nucleophiles under rather mild conditions where

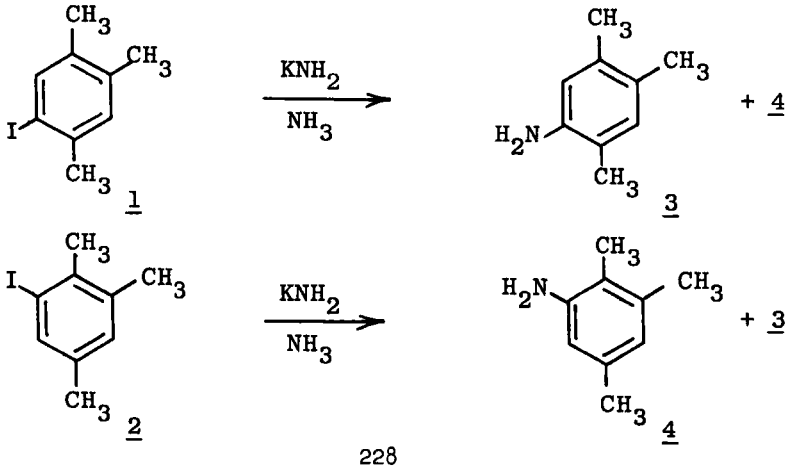
aryne formation is possible, such reactions frequently suffer from cine-substitution leading to isomeric products because of nonregiospecific formation and/or reactions of the intermediate aryne.[2,4,6]

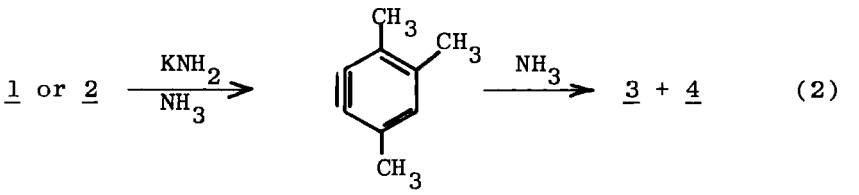
The purpose of the present article is to review the synthetic potential of a new method for aromatic nucleophilic substitution which has the following characteristics:

1) does not require activated substrates
2) proceeds in a completely nonrearranging manner
3) takes place via a mechanism not previously recognized in aromatic systems.

II. THE $S_{RN}1$ MECHANISM. DISCOVERY AND BACKGROUND

In 1970 Bunnett and Kim reported[7] that the reaction of 5- and 6-iodopseudocumenes (1 and 2, respectively) with KNH_2 in liquid ammonia afforded significantly more of the direct substitution products (3 and 4, respectively) than could be rationalized by assuming that amination was proceeding exclusively via the common aryne 5 (eq. 2).





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These results raised the possibility that a substitution pathway other than the aryne mechanism could be operating. The well known addition-elimination (S_NAr)[3] mechanism seemed unlikely, since it was unprecedented for unactivated substrates such as 1 and 2. The marked decrease in the amount of direct substitution product observed in the presence of catalytic amounts of radical scavengers lead to the proposal that a significant fraction of the nonrearranging substitution was occurring via a radical-chain mechanism, which Bunnet and Kim designated as $S_{RN}1$ (substitution, radical-nucleophilic, unimolecular).[7] The steps comprising a typical $S_{RN}1$ reaction are outlined in Scheme I for an aromatic substrate containing nucleofugic group (X) reacting with a nucleophile (Y^-).

Scheme I

$$\text{Ar-X} + \text{electron donor} \longrightarrow [\text{Ar-X}]^{\cdot -} + \text{donor residue} \quad (3)$$

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

$$\text{Ar}\cdot + \text{Y}^- \longrightarrow [\text{Ar-Y}]^{\cdot -} \quad (5)$$

$$[\text{Ar-Y}]^{\cdot -} + \text{Ar-X} \longrightarrow \text{Ar-Y} + [\text{Ar-X}]^{\cdot -} \quad (6)$$

Initiation of the chain reaction is effected by electron transfer from a suitable donor to the substrate (eq. 3).

The resulting radical anion expels the nucleofugic group with a pair of electrons to form an aryl radical and X^- (eq. 4). Formation of the new carbon-nucleophile bond is accomplished by combination of the aryl radical with nucleophile Y^- to form a radical anion (eq. 5), which then transfers an electron to a neutral substrate (eq. 6). This affords the observed substitution product [Ar-Y] and another substrate radical anion, which can reenter the propagating cycle in eq. 3. The separate components of this radical-chain sequence have ample precedent, and the overall reaction scheme is analogous to that proposed earlier by Kornblum[8,9] and Russell[10] for reactions of nucleophiles with certain p-nitrobenzyl halides and 2-halo-2-nitropropanes. However, prior to 1970 such a reaction mechanism was unheard of in the area of nucleophilic aromatic substitution.

Although the $S_{RN}1$ reactions mentioned above, as well as a number of analogous radical-chain substitutions at saturated carbon,[9] proceed reasonably well without the aid of catalytic reagents, it has been determined that most aromatic $S_{RN}1$ reactions require catalysis by alkali metal[11] or near-ultraviolet light.[12] The metal provides solvated electrons in liquid ammonia, which in turn initiate the chain reaction by reducing the aromatic substrate to its radical anion. The exact catalytic function of Pyrex-filtered light is still uncertain, although evidence has been presented to support the theory that it may cause electron transfer from the nucleophile to the substrate through an intermediate charge-transfer complex.[13]

The annoying dehalogenations of aryl halide substrates and reductions of substitution products which often accompany alkali metal-promoted reactions can usually be circumvented by excluding the metal catalyst and simply irradiating the reactants in liquid ammonia with an external tungsten bulb, or preferably with 350 nm lamps in a Rayonet photochemical reactor.[14]

III. SCOPE AND LIMITATIONS

Before proceeding with a survey of specific examples of aromatic $S_{RN}1$ reactions in synthesis, it is appropriate to briefly consider the current range of applications with regard to the following:

1) nucleofugic groups which can be displaced
2) substituents which are compatible with the reaction mechanism
3) aromatic substrates which give up their nucleofugic groups
4) types of nucleophiles which participate
5) reaction solvents.

A detailed discussion of the mechanistic rationalizations for the limitations of aromatic $S_{RN}1$ reactions may be found in a recent review by Bunnett.[15]

Halogens can serve as satisfactory nucleofugic groups. The relative ease of displacement is I > Br > Cl > F. The difference in reactivity between aryl iodides and bromides is usually small enough to make either of these substituents useful in synthesis. Other groups found to undergo facile displacement include SPh,[16] NMe_3^+[16] and $\ominus PO(OEt)_2$[16-18]

Substituents other than the nucleofugic group can have a definite influence on aromatic $S_{RN}1$ reactions. For example, a nitro group, although it ranks as one of the best activating groups in S_NAr reactions and $S_{RN}1$ substitutions at saturated carbon,[9] is incompatible with aromatic $S_{RN}1$ reactions. Other groups which also interfere with the substitution reaction include the hydroxyl and dialkylamino substituents.[19,20] Alkyl, alkoxy, phenyl, carboxylate, and benzoyl groups allow $S_{RN}1$ reactions to proceed in a normal fashion.[19] Alkyl substituents ortho to the nucleofugic substituent exert little steric hindrance to substitution under $S_{RN}1$ conditions.[21,22]

A variety of carboaromatic substrates equipped with suitable nucleofugic groups participate in $S_{RN}1$ reactions. These include simple benzene derivatives, halogenated naphthalenes,[19,20,23-25] antracenes,[19] and phenanthrenes.[19] A number of halogenated heterocycles including 2-,3- and 4-halopyridines,[20,26] 2-halopyrimidines,[27] 2-chloropyrazine,[27] 2-chloroquinoline,[28-30] haloisoquinolines,[31,32] and halogen derivatives of thiophene[33] react satisfactorily. Certain vinyl halides also undergo substitution via the $S_{RN}1$ pathway.[34]

Nucleophiles which have received the most attention in aromatic $S_{RN}1$ reactions include carbanions derived from simple ketones,[12,16,19,23,26-30,35,36] nitriles,[20,23,37] 2- and 4-picolines,[38] and conjugated hydrocarbons.[35] Sulfanions of aromatic[24,31,39] and aliphatic[23,40] thiols react satisfactorily as do certain phosphanions such as those formed from dialkyl phosphites[25,41] and diarylphosphines.[42] The only nitranion species which has been found to be generally satisfactory as a nucleophile is amide $(NH_2)^-$ ion. A number of

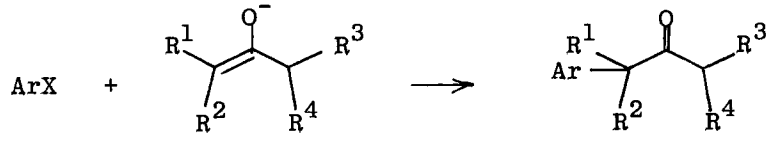
other nucleophiles such as the ions derived from alcohols, phthalimide, and acetylenes have proved to be unsatisfactory.

Consideration of various solvents for $S_{RN}1$ reactions has led to the conclusion that liquid ammonia is the most satisfactory for preparative experiments.[43] Dimethyl sulfoxide (DMSO)[13,36,43] appears to be a reasonably attractive alternative to liquid ammonia. Aqueous tert-butyl alcohol has been employed for reactions of phenoxide ion with halo benzenes, using sodium amalgam to promote the substitution process.[44]

IV. SYNTHETIC APPLICATIONS

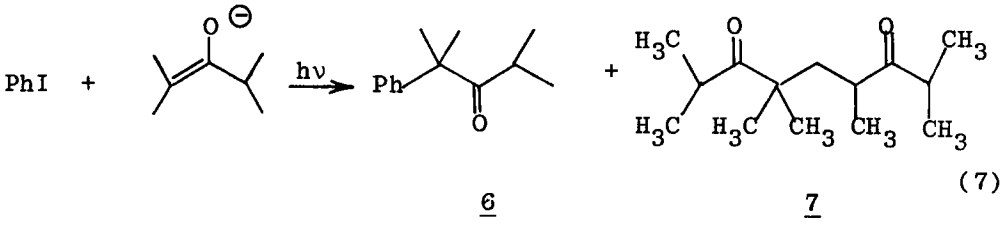
A. Preparation of α-Aryl and α-Hetaryl Ketones

Alkylation of ketone enolates is one of the mainstays of organic synthesis.[45] However, arylation of enolates is much more difficult owing to the notoriously poor performance of unactivated aryl halides in reactions with carbanions. With the discovery[16] that ketone enolates are willing nucleophilic participants in aromatic $S_{RN}1$ reactions, many of the problems once associated with enolate arylation have now been supplanted by a convenient, general method for introducing various aryl and hetaryl substituents at the α-carbon of ketones. The following general equation is useful for illustrating the type of reactions which have been studied and for considering the limitations associated with such reactions.



The best procedure for conducting enolate arylations involves generation of the carbanion by means of potassium amide or potassium t-butoxide in liquid ammonia[12] followed by addition of the aromatic substrate and photostimulation.[12,22,30]

The major limitation of these reactions lies in the nature of the enolate. For example, enolates that contain β-hydrogens, such as potassio 2,4-dimethyl-3-pentanone, undergo a competing hydrogen atom transfer with the phenyl radicals generated under $S_{RN}1$ conditions, to produce appreciable amounts of benzene and diketone 7, along with the expected α-phenyl ketone 6 (eq. 7).[46]

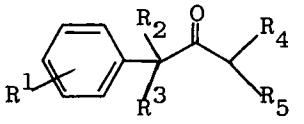


6 7 (7)

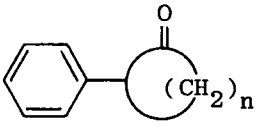
Enolates from alkyl aryl ketones such as acetophenone and propiophenone react poorly with aryl and hetaryl halides, presumably because the radical anions generated by combination of aryl and hetaryl radicals with the respective enolates are too stable to transfer an electron to the original substrate.[22,26,46]

The steric bulk of the enolate seems to play only a minor part in the overall facility of the reaction, although bulky groups at positions ortho to the nucleofugic substituent will block substitution with hindered enolate anions.[19]

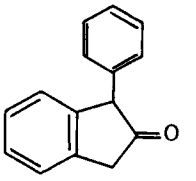
Within the framework of the preceding enolate requirements and the general limitations of aromatic $S_{RN}1$ reactions (Sec. II), the following ketones have been prepared.



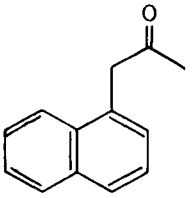
(Ref. 12,16,19,22,23,35)



n = 2-6
(Ref. 22)



(Ref. 22)



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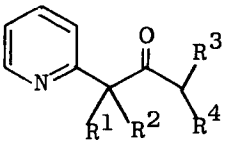

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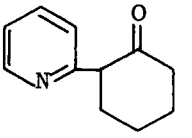

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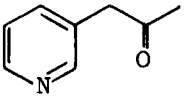
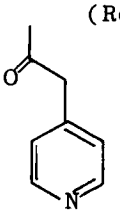
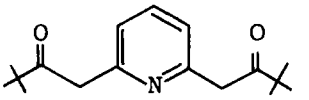


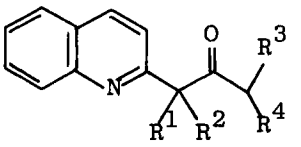
(Ref. 26)



(Ref. 26)



(Ref. 26)



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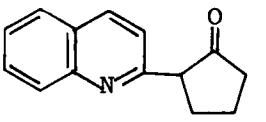
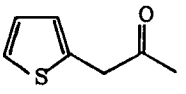
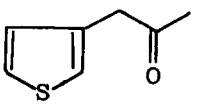


(Ref. 30)

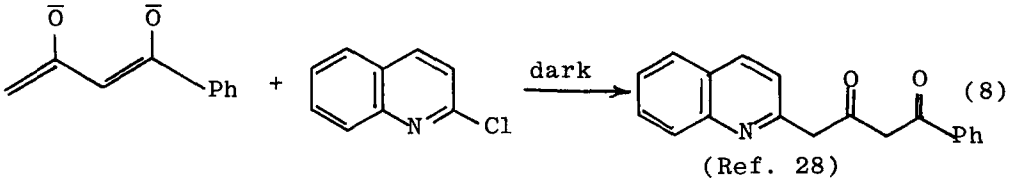


(Ref. 33)



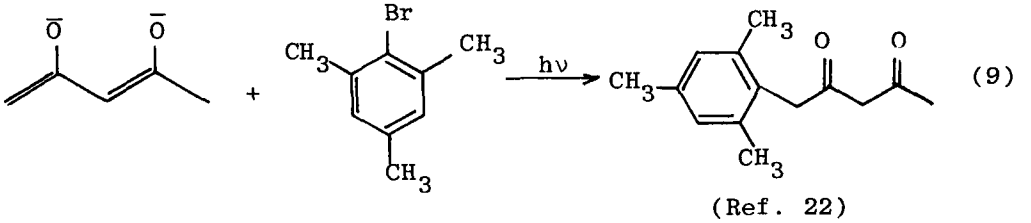
(Ref. 33)

Although monoanions of β-diketones fail to undergo $S_{RN}1$ reactions with aryl[22] and hetaryl halides,[30] 1,3-dianions of β-diketones can be arylated at the terminal carbanion site as shown in eqs. 8 and 9.



(8)

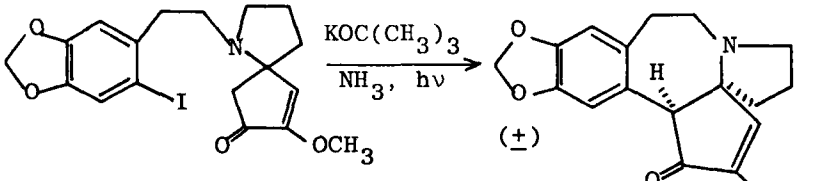
(Ref. 28)



(9)

(Ref. 22)

An interesting type of enolate arylation, which has yet to be explored fully, involves intramolecular $S_{RN}1$ reactions to form cyclic ketones. An elegant application of this procedure is found in the formation of (±) cephalotaxinone (9) from iodo ketone 8.[47] The ring closure may

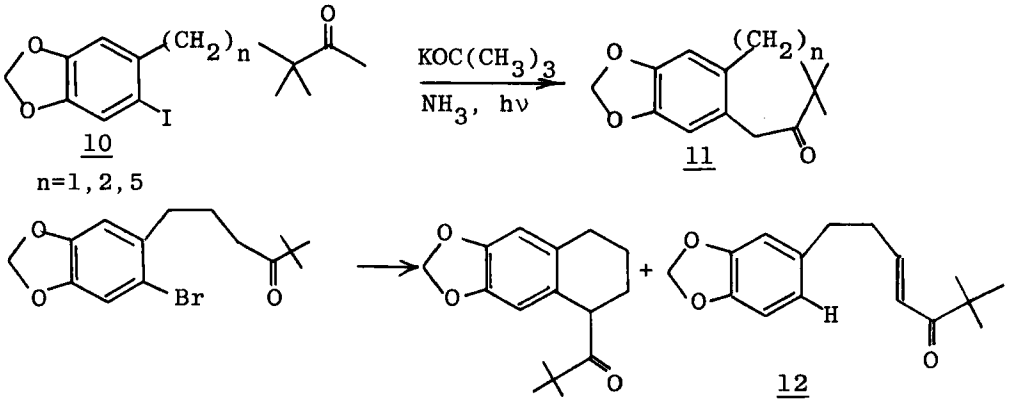


8 (±) 9

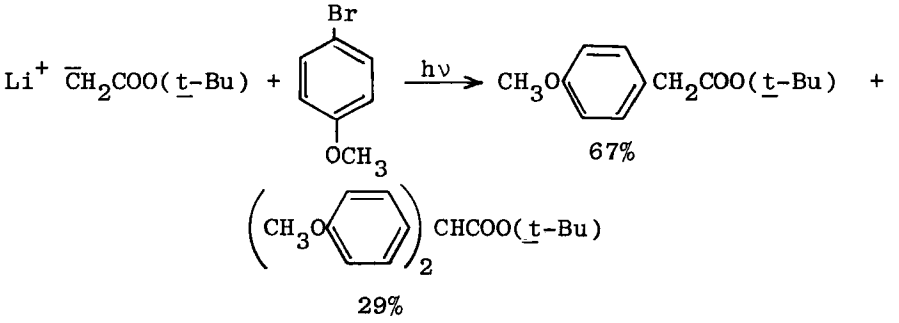
94%

be stereospecific, but in any case, equilibration under the basic conditions would give the more stable configuration obtained.

Intramolecular arylation of enolates from iodophenyl ketones 10 has recently been found to proceed smoothly under conditions of photostimulation to afford cyclic ketones 11.[48] Depending upon the structure of the starting ketone, intramolecular hydrogen atom transfer occurs to form mainly α,β-unsaturated ketones such as 12.

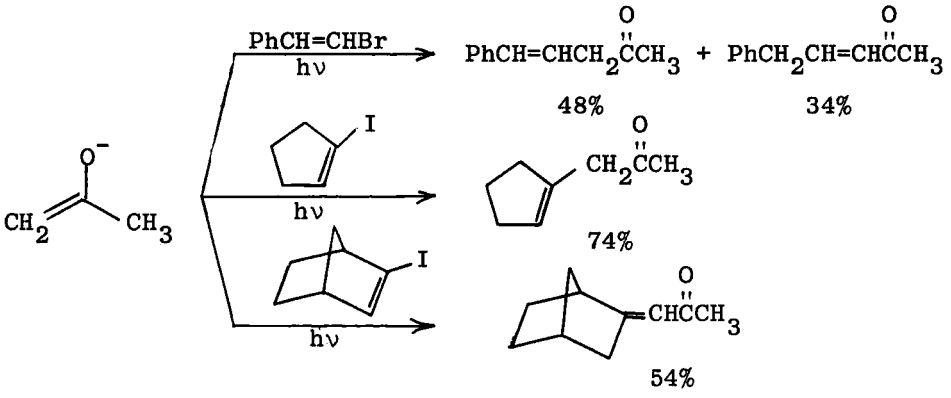


The lithium enolate of tert-butyl acetate has been reported[48] to undergo arylation with p-bromoanisole, but the synthesis of α-aryl esters via $S_{RN}1$ reactions has yet to be explored in detail.



B. Preparation of α,β- and β,γ-Unsaturated Ketones

Vinyl halides undergo photostimulated reaction with acetone enolate to form mixtures of α,β- and β,γ-unsaturated ketones.[34] The former products undoubtedly arise from tautomerization of the initially formed β,γ-unsaturated isomers. The following examples are representative.

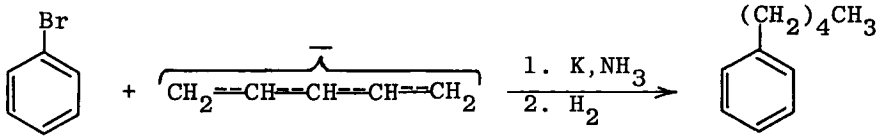


C. Preparation of Alkyl Benzenes

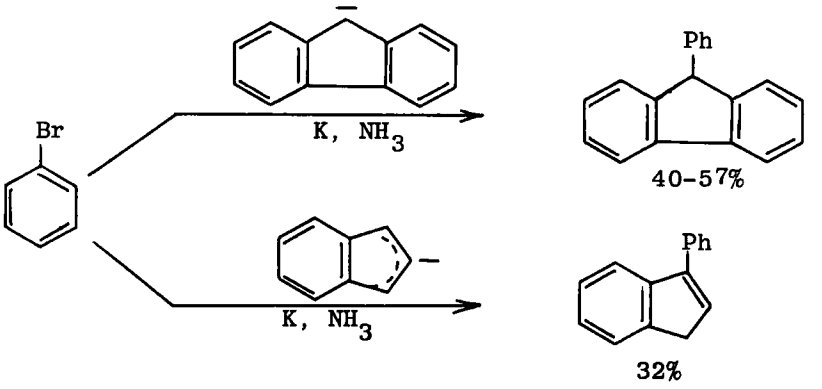
Establishment of a hydrocarbon side chain on an aromatic nucleus can be accomplished by the $S_{RN}1$ reaction, thus providing a nucleophilic alternative to Friedel-Crafts alkylation. Although applications of this new method for aromatic alkylations are somewhat limited, the following examples illustrate the two basic approaches utilized to date. The first of these involves hydrocarbon anions as nucleophiles and the second employs carbanions derived from nitriles.

Reaction of bromobenzene with the carbanion of 1,3-pentadiene in the presence of potassium metal affords a mixture of monophenylated pentenes and pentadienes, as well as

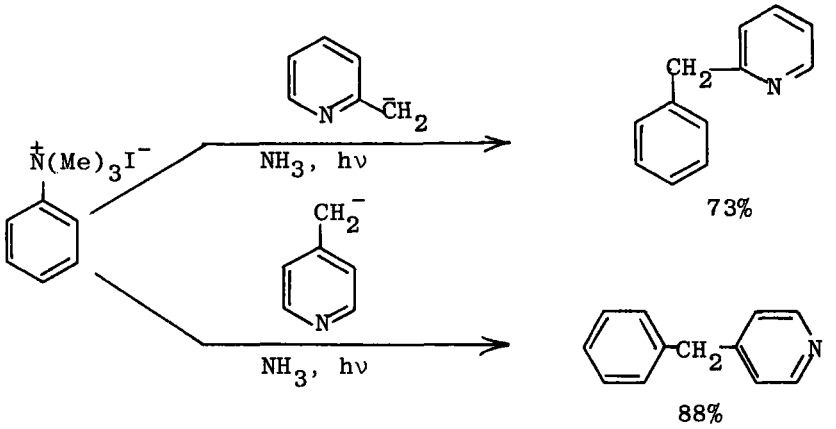
products resulting from attachment of two or three phenyl groups to the hydrocarbon chain. When the reaction is carried out at -78° and the crude product mixture subjected to catalytic reduction, 1-phenylpentane is obtained in 74% yield.[35]

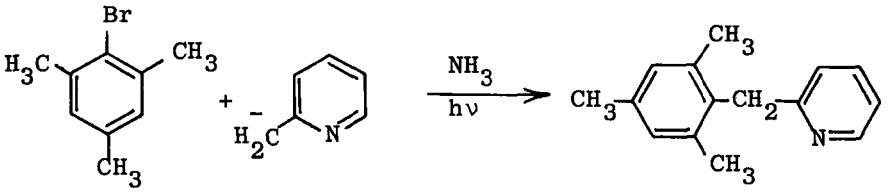


The carbanion from fluorene reacts satisfactorily with bromobenzene to give mainly 9-phenylfluorene, along with a small amount of 9,9-diphenylfluorene.[35] The carbanion from indene affords mainly 3-phenylindene.[35] Treatment of phenyltrimethyl-



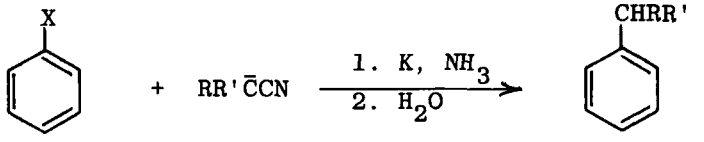
ammonium iodide with the carbanions from 2- and 4-picoline under photostimulation results in attachment of 2- and 4-pyridylmethyl groups to the benzene nucleus as shown below.[38] Similarly, bromomesitylene reacts with 2-picolyl anion to form (2-pyridylmethyl) mesitylene in 87% yield.[38]





When various benzene derivatives containing appropriate nucleofugic groups are allowed to react with nitrile carbanions, there is a tendency for the radical anion formed by combination of phenyl radical and the nitrile carbanion to expel cyanide ion; thereby giving rise to a complex mixture of products derived from radical coupling and reduction.[37] Because of the extensive amount of decyanation, these reactions are not suitable for the synthesis of α-arylnitriles. However, they can be used with moderate success to attach an alkyl group to a

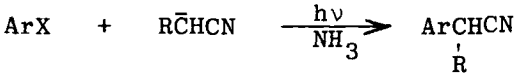
benzene ring in place of a nucleofugic group, if the reaction mixture is quenched with water while excess metal is still present to facilitate decyanation. This procedure, which is illustrated in the eq. 10 has been used to introduce ethyl, propyl, isopropyl, butyl, isobutyl and benzyl groups. Yields range from 20-50%.[37]



(10)

X = I, Br, Cl, F, $OPO(OEt)_2$, NMe_3^+

Interestingly, when nitrile carbanions are allowed to react with 1-halonaphthalenes,[23] 2-chloropyridine,[20,49] and 2-chloroquinoline[49] under the influence of near-ultraviolet light, decyanation does not occur, and the respective α-naphthyl and α-hetaryl nitriles are obtained in good yields (eq. 11).



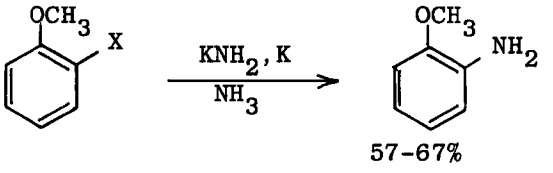
(11)

Ar = 1-naphthyl, 2-pyridyl, 2-quinolyl

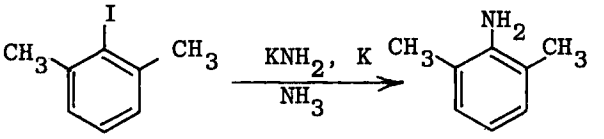
D. Preparation of Aromatic Amines

In spite of the fact that the aromatic $S_{RN}1$ reaction was discovered during the amination of iodopseudocumenes, relatively few examples of $S_{RN}1$ aminations of aryl or hetaryl halides have been reported. A potentially attractive role for such reactions can be found in the direct amination of substrates

which normally react with amide ion to afford rearranged aryne products or which fail to react by elimination-addition because the positions ortho to halogen have no ionizable hydrogens. The following metal promoted reactions illustrate these two approaches.[11]



57-67%



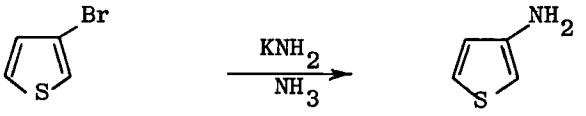
64%

The most generally useful $S_{RN}1$ amination procedure reported to date involves reaction of aryl diethyl phosphates with KNH_2 and potassium metal in liquid ammonia to form the corresponding anilines in good yields.[17] Since the requisite phosphate esters (Toxic!) can be prepared easily from phenols, the overall sequence provides a new method for the conversion of phenols to anilines as shown in eq. 12. The established

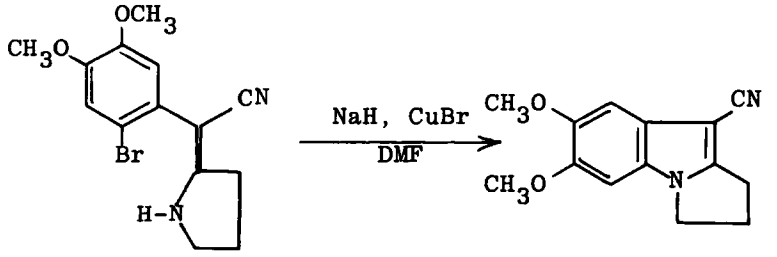
$$\mathrm{ArOH} \xrightarrow[\mathrm{NaOH}]{(\mathrm{EtO})_2\mathrm{POCl}} \mathrm{ArOPO(OEt)_2} \xrightarrow[\mathrm{NH_3}]{\mathrm{K},\ \mathrm{KNH_2}} \mathrm{ArNH_2} \quad (56\text{-}78\%) \tag{12}$$

nucleofugic character of the $OPO(OR)_2$ group, coupled with its ease of introduction, implies that the scheme shown above could be expanded to include nucleophiles other than amide.[37] This would provide a general method for displacement of aromatic hydroxyl groups, a traditionally difficult and rare synthetic operation.

3-Bromothiophene reacts with KNH_2 in an uncatalyzed $S_{RN}1$ process to form 3-aminothiophene in 79% yield. 2-Bromothiophene affords mainly 3-aminothiophene.[33]



Conjugate bases of aryl amines react poorly with aryl halides under the influence of alkali metals.[11] Photostimulated aminations have not been sufficiently probed to conclusively test their generality. For example, attempted ring closure of 13 under photo-$S_{RN}1$ conditions employing potassium tert-butoxide in liquid ammonia afforded the desired cyclization product (14) in only 2% yield.[50]

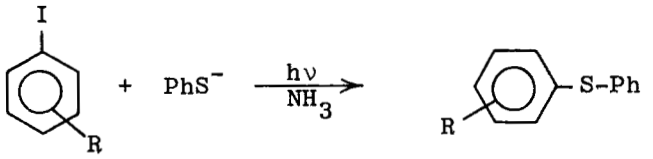


13 14

When the cyclization was conducted using sodium hydride in refluxing dimethylformamide with copper (I) bromide as a catalyst, 14 was obtained in 60-70% yield.

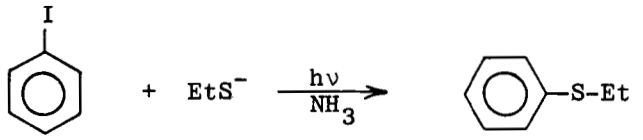
E. Preparation of Aryl Sulfides

Iodobenzenes react with benzenethiolate ion in liquid ammonia under irradiation to afford diaryl sulfides in good yields.[24,40] This procedure is considerably milder than

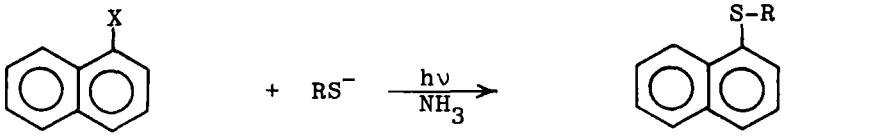


traditional substitution methods leading to diaryl sulfides.

Photostimulated reaction of ethanethiolate ion with iodobenzene proceeds slowly to produce only 30% of ethyl phenyl sulfide.[40] The modest yield is attributed to the tendency for the radical anion of ethyl phenyl sulfide to fragment to form thiophenoxide ion and ethyl radical. In contrast to this,



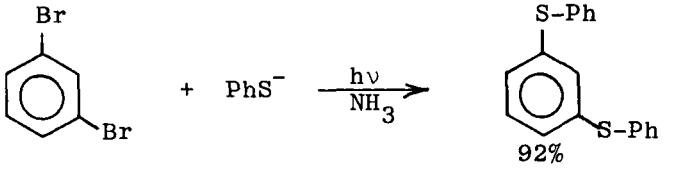
1-halonaphthalenes react smoothly with alkyl mercaptide ions to give alkyl naphthyl sulfides in excellent yields.[23]



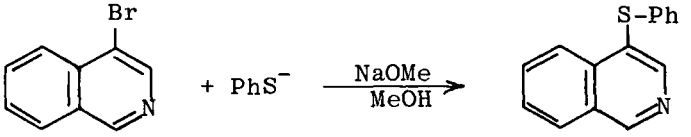
X = Cl, I

R = $\underline{n}$-C_4H_9, CH_2CH_2OH

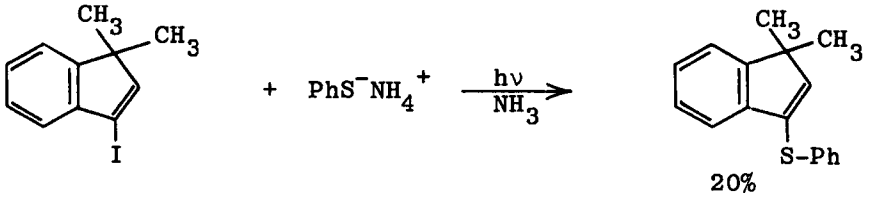
Dihalobenzenes undergo photostimulated disubstitution with thiophenoxide to form bis sulfides in yields of 55-95%.[39] The type and relative positions of the halogens have only a minor effect on bis sulfide formation, which occurs without significant accumulation of the monosubstitution product.

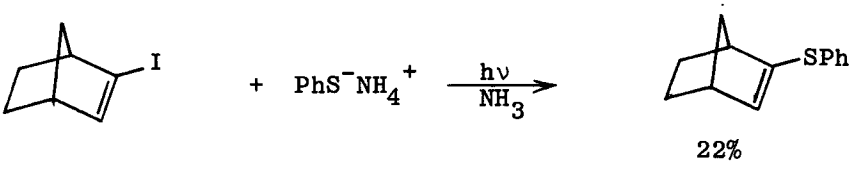


4-Bromoisoquinoline reacts with sodium thiophenoxide to form phenyl 4-isoquinolyl sulfide in good yield when the reaction is carried out at 147° in the presence of sodium methoxide.[31] In this case methoxide ion promotes the $S_{RN}1$ reaction.

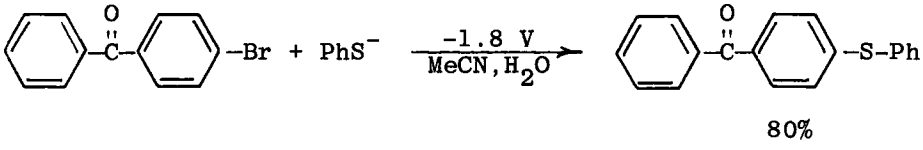


Preparations of aryl vinyl sulfides by $S_{RN}1$ reactions of ammonium thiophenoxide with vinyl halides have been moderately successful.[34]



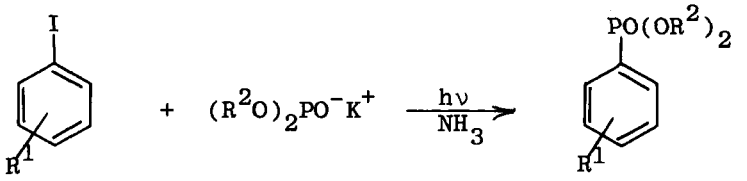


Recently it has been reported[51-53] that aromatic $S_{RN}1$ reactions involving benzene thiolate ion and halogeno derivatives of acetophenone, benzophenone, benzonitrile, and naphthalene can be induced electrochemically. The few preparative experiments which were conducted indicate that this could be a viable synthetic procedure.

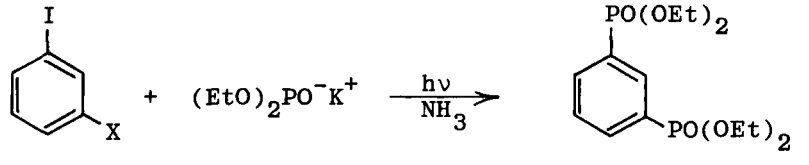


F. Preparation of Dialkyl Aryl Phosphonates and Triaryl Phosphines

Photostimulated reactions of aryl iodides with potassium dialkyl phosphites afford dialkyl aryl phosphonates in yields of 87-96%.[25,41] It is interesting to note that



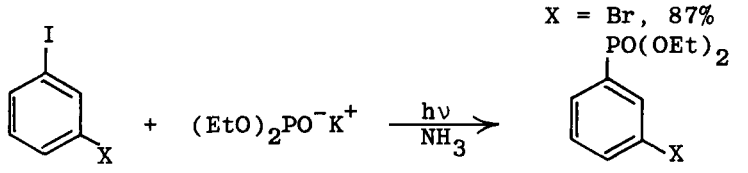
m-diiodobenzene and m-bromoiodobenzene give mainly the diphosphonate ester with potassium diethyl phosphite, while m-chloroiodobenzene and m-fluoroiodobenzene are converted to the monophosphonates.[25]



X = I, Br

X = I, 94%

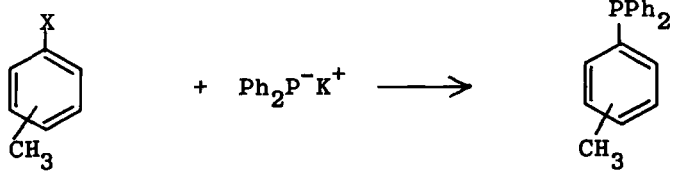
X = Br, 87%



X = Cl, 89%

X = F, 96%

A recent study with phosphanion nucleophiles has demonstrated that m- and p-iodotoluene as well as m- and p-bromotoluene react with potassium diphenylphosphide in liquid ammonia or DMSO to afford the appropriate diphenyltolylphosphines in good yields.[42]

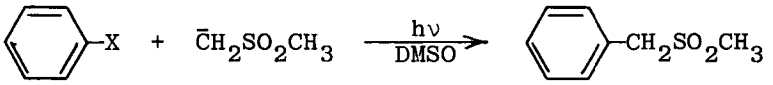


X = I, Br

CH_3 = m, p

G. Miscellaneous Reactions

Reactions of sulfur stabilized carbanions with aryl halides under $S_{RN}1$ conditions have received little attention in spite of their obvious synthetic potential. The discovery[54] that dimsyl ion reacts with phenyl halides in DMSO solution upon exposure to sunlight provides an interesting precedent for further research.



X = I, Br, Cl

H. Comments on General Experimental Procedures

Detailed procedures for metal promoted and photostimulated $S_{RN}1$ reactions may be found in a number of the papers cited in the previous discussion.

Preparative reactions using 10-20 mmol of aromatic or heteroaromatic substrate and 10-60 mmol of the appropriate nucleophile are normally conducted in 250-350 ml of liquid ammonia. A 500 ml three-necked Pyrex flask equipped with a Dry Ice/2-propanol condenser, pressure equilizing addition funnel nitrogen inlet, and mechanical stirrer is satisfactory for photostimulated reactions. A flask of this size and configuration can be lowered into the top of a Rayonet model RPR-208 photochemical reactor far enough to provide sufficient illumination for most photostimulated reactions. More efficient

irradiation, and thus shorter reaction times, can be obtained by using a cylindrical, flat-bottomed Pyrex reaction flask measuring 10.6 cm x 50 cm topped by a 34/45 ℠ female joint. A second 34/45 ℠ male joint, to which are attached 24/40 ℠ female joints for the Dry-Ice condenser, addition funnel and nitrogen inlet, serves as a cover. Stirring is accomplished by means of a glass-coated magnetic stirring bar.

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