NUCLEOPHILIC SUBSTITUTION IN AROMATIC SYSTEMS

Z. A. MALIK

UNIVERSITY OF ISLAMABAD
PRESS

Rs. 20.00

NUCLEOPHILIC SUBSTITUTION IN AROMATIC SYSTEMS

by
Z. A. MALIK
D. Phil (York)

UNIVERSITY OF ISLAMABAD
PRESS

UNIVERSITY OF ISLAMABAD

OCTOBER 1974

PRICE
Pak. Rs. 20.00

PUBLISHED BY : UNIVERSITY OF ISLAMABAD PRESS

ORDERS : MANAGER.
BOOK-SHOP & PUBLICATION CELL,
UNIVERSITY OF ISLAMABAD
ISLAMABAD (PAKISTAN)
TELE : 21028
CABLE : UNIVERSITY

PREFACE

Understanding of basic concepts, with logical conclusions is an important factor for learning and teaching of organic chemistry. With this view recent developments in the field of nucleophilic substitutions in aromatic systems are considered in the light of experimental results available in chemical literature. The monogragh deals with nucleophilic displacements on benzene and its polycyclic systems, nonbenzenoid aromatics and heterocyclic systems including arynes and Meisenheimer complexes. Generalised form of reaction schemes are illustrated and discussed with the view to help reader in understanding the subject with a systematic approach. Breakdown pattern of the reaction intermediates are particularly emphasized. Various polarising factors demanding structures and reactivity relationship are included alongwith some rearrangement reactions pertaining to this class of reactions.

I would like to acknowledge my thanks for the understanding I have received from my wife during the preparation of this monograph and in particular to Dr. Rashid Iqbal for reading whole of the manuscript and stimulating discussions. I feel indebted to Dr. Afzal Ahmad for reading a portion of this volume and his critical suggestions. I should like to express my gratitude to Dr. M.Afzal, Chairman Department of Chemistry for encouragement during the preparation of this monograph. I am also obliged to my students who over the past years helped in collecting the research information and to Mr. M. Akbar for drawings and sketches.

University of Islamabad
May 1974.

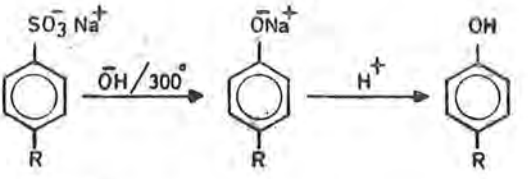
(Dr. Z. A. Malik)

CONTENTS

NUCLEOPHILIC SUBSTITUTION IN AROMATIC SYSTEMS

Introduction :

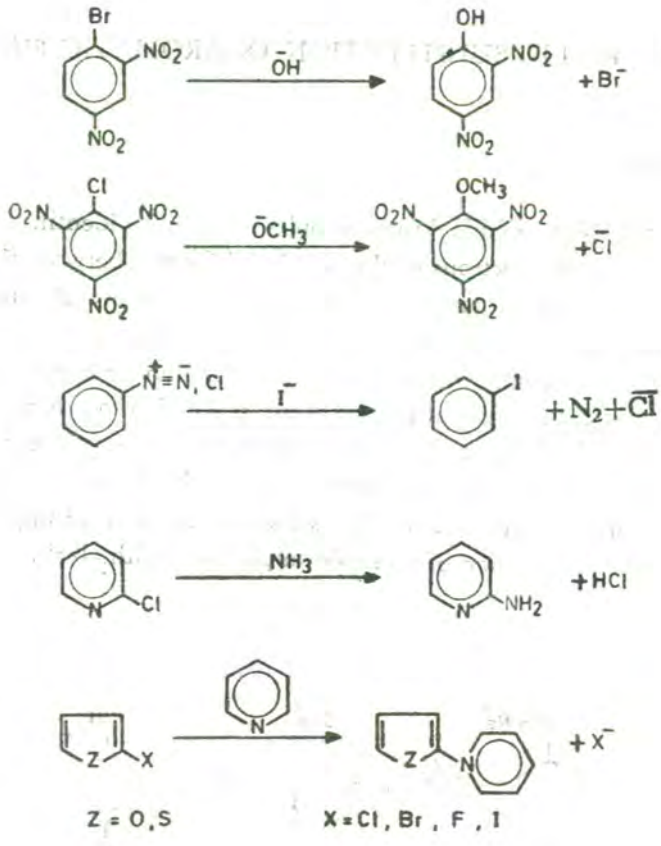
The term 'Nucleophilic Aromatic Substitution' is identified in which one or both of the electrons of the new bond formed between the entering substituent and the aromatic nucleus are supplied by the nucleophile. These substituents are groups of atoms. Such reactions are often referred as displacement reactions and occur with difficulty under normal conditions. The electron-attracting substituents at o- or p-position on benzene or the hetero atom (O, N, S) in the hetero-aromatic ring facilitate these reactions. In the absenee of such structural features extremely vigorous conditions are necessary in order to bring about the substitution. For example, phenols are produced by the fusion of aromatic sulphonates with alkali.



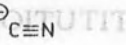
R = H, CH_3

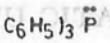
In these substitutions the displaced group is an anion and thus the reaction becomes facile if the anion displaced is sufficiently stable such as halogens, nitro group, sulphonates and alkoxyl group.

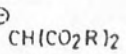
The reaction of 1-bromo-2, 4-dinitrophenol with alkali to give 2, 4-dinitrophenol is a familiar reaction. 1-Bromo-2, 4-dinitrophenol also reacts readily with other nucleophilic reagents to give the corresponding 2, 4-dinitrobenzene derivatives. The displacement of hydrogen as hydride ion (H^-) is rare due to the instability of the anion. The general nature of these substitutions should become clear from the following examples :

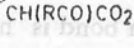


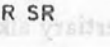
The nucleophilic reagents are anions or neutral molecules with dipoles (Table I). The negative end of the molecule possessing a free electron pair attacks at the point of lowest density or at a positive centre over the aromatic nucleus. The substituents attached to the benzene ring are usually electron-attracting groups with —M effect conjugated with the aromatic system. They are $-NO_2$, $C\equiv N$, $>C=O$, $-\overset{+}{N}\equiv N$, —COOR, —COOH, —COR or $-SO_2OH$ and are expelled with the bonding electrons. Since these groups are possessing π electrons and capable to interact with delocalised π-orbital of the aromatic nucleus thus profoundly influence its activity. The withdrawal of electrons from a neighbouring group is described as having —M effect, where M stands for mesomeric and negative sign indicates the electron-withdrawing nature of the group.

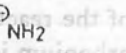


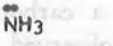


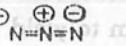


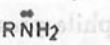


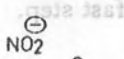


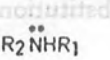


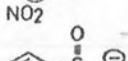


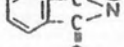


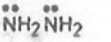


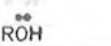


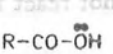


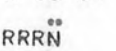












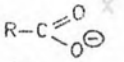


TABLE I

NUCLEOPHILE	NUCLEOPHILIC AGENT
$\overset{\ominus}{C}\equiv N$	$(C_6H_5)_3\ddot{P}$
$\overset{\ominus}{C}H(CO_2R)_2$	$\overset{\oplus}{Na}\ \overset{\ominus}{R}$
$\overset{\ominus}{C}H(RCO)CO_2R$	$R\ddot{S}R$
$\overset{\ominus}{N}H_2$	$\ddot{N}H_3$
$\overset{\ominus}{N}=\overset{\oplus}{N}=\overset{\ominus}{N}$	$R\ddot{N}H_2$
$\overset{\ominus}{N}O_2$	$R_2\ddot{N}HR_1$
	$\ddot{N}H_2\ddot{N}H_2$
$\overset{\ominus}{O}H$	$H_2\ddot{O}$
$\overset{\ominus}{O}R$	$R\ddot{O}H$
$\overset{\ominus}{S}H$	$R-CO-\ddot{O}H$
$\overset{\ominus}{S}R$	$RRR\ddot{N}$
$R-C\begin{smallmatrix}=O\\ \diagdown O^{\ominus}\end{smallmatrix}$	
$\overset{\ominus}{X}$	

R= Alkyl group, X= Cl, Br, I.

AROMATIC UNIMOLECULAR SUBSTITUTIONS
(SN_1 MECHANISM)

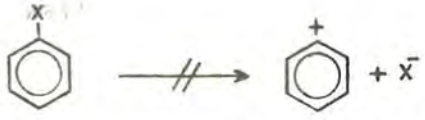
For several tertiary alkyl halides carbon-halogen bond is heterolytically cleaved to yield a carbonium ion in the slow step of the reaction. First-order kinetics are observed for such processes. The carbonium ion produced acts with a nucleophile present in the reaction medium to yield the nucleophilic aliphatic substitution product in a subsequent fast step.

$$R_3C{-}X \rightleftharpoons R_3C^{+} + X^{-}$$

$$R_3C^{+} + Nu^{-} \longrightarrow R_3C{-}Nu$$

R = Alkyl group X = Cl, Br, I

Halobenzenes do not react in this manner under similar conditions to produce aryl action.



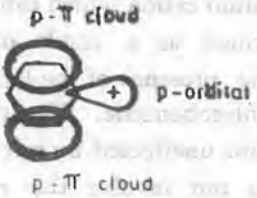
The very high activation energy required for the reaction is manifold :—

a. The carbon-halogen bond in aryl halide is much stronger as compared to aliphatic halide. This is revealed by the shorter bond length in chlorobenzene :

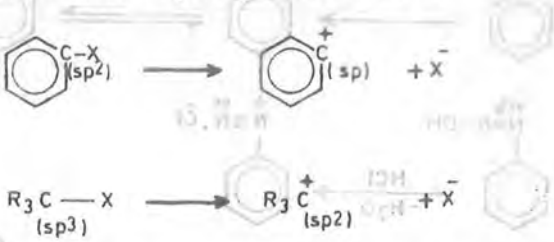
COMPOUND	C-Cl BOND LENGTH
C_6H_5Cl	1.70 A°
$(CH_3)_3CCl$	1.78 A°

b. Bond to the leaving group is much stronger in $Ar{-}X$ than in $R_3C{-}X$ because the former is usually associated with conjugation of unshared electrons on X with the aromatic ring and this becomes an unfavourable heterolytic requirement.

c. The aryl carbonium ion formed by the heterolysis of Ar−X can not stabilise itself in the internal cojugation of the system because the vacant p−orbital is at right angles to the rest of the p π −orbitals and can not overlap :

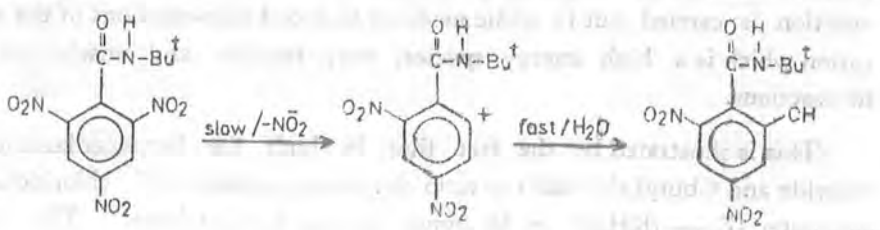


d. The instability of the aryl carbonim ion can also be related to the greater electronegativity of the sp−like carbon atom that bears the vacant p−orbital and the positive charge in the carbonium ion as compared to sp^2−hybridised carbon of the aliphatic carbonium ion.

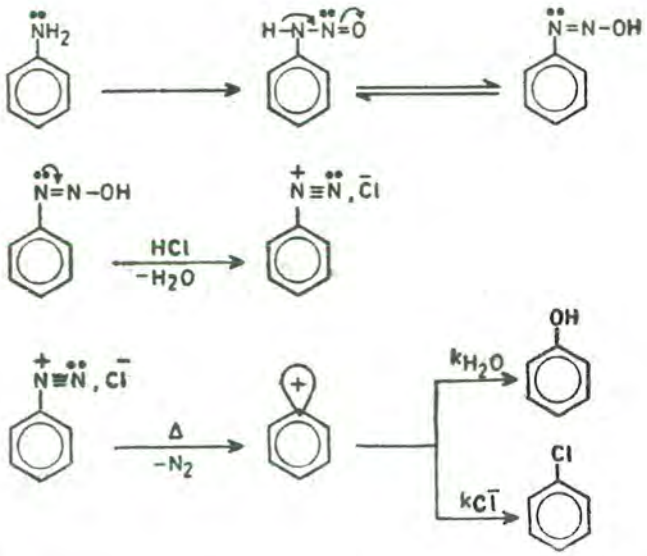


e. The positive charge of the aryl carbonium ion is much less exposed to solvation due to its cage-like structure than that of the alkyl or side-chain aryl cations.

f. Steric environments are not very important in forming aryl cation as they are in aliphatic unimolecular nucleophilic displacement reactions. However high temperature hydrolysis of o-and p-halogenophenols in alkaline medium are proposed to undergo unimolecular nucleophilic reactions but less well documented. Unimolecular mechanism is known for some nucleophilic aromatic rearrangments. For instance, in alkaline medium N-tert-butyl-2-4, 6-trinitrobenzamide liberates nitrite ion in a reaction of zeroth orper.



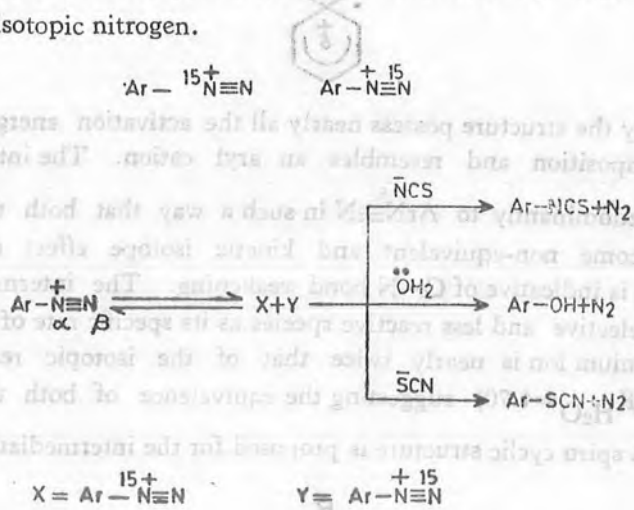
Although unimolecular nucleophilic substitution reactions of aromatic compounds are not very common and they can not occur under normal conditions, yet the most commonly known of these reactions are the thermal hydrolysis of aryl diazonium salts. Thus, heating aniline with nitrous acid gives a benzene-diazonium cation which can be decomposed by heating in water and phenol is formed as a result of nucleophilic substitution reacrion. However, in the presence of the large concentration of chloride ion the product is largely chlorobenzene. The rate of decomposition of the diazonium compound remains uneffected by salt effect and shows that the rate-determining step does not involve the nucleophile thus supports an SN_1 mechanism.



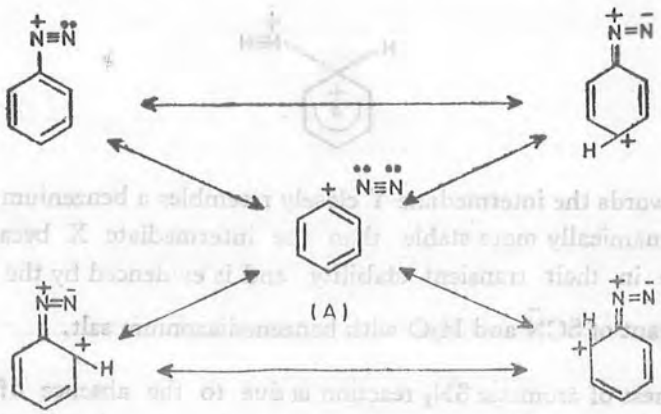
The rate of disappearance of the benzenediazonium ion is only dependent of the concentration of the aryl cation because the decomposition produces a very unstable cation and stable diatomic nitrogen molecule at the same time, therefore, the energy required for the formation of the cation is counter-balanced by the energy gained in the formation of nitrogen. The reaction is carried out in acidic medium to avoid side-reactions of the aryl cation which is a high energy species, very reactive and unselective in its reactions.

This is illustrated by the fact that in both the benzenediazonium chloride and t-butyl chloride the ratio of the rate constant with chloride ion and water (K_{Cl^-}/KH_2O) is 60 times greater for the later. The low

reactivity of the aryl cation is due to the recombination of the ion with rearranged feably nucleophilic nitrogen as shown by diazonium salts containing isotopic nitrogen.

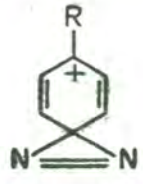


in which intermediate X is highly reactive and unselective species of high energy. ($K_{SCN^-}/K_{H_2O}=2.8$). It is suggested that this intermediate exists in a vibrationally excited state of the diazonium ion with weak C—N_α bond having (A) as the main structure and would not require much assistance from the ring electrons and can achieve a transition state by itself in such a way that C—$\overset{+}{N}\equiv N$ distance is rather large and

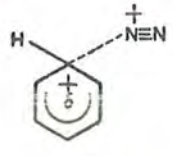


as a result small fractional charge is introduced into the aromatic nucleus.

Presumably the structure possess nearly all the activation energy necessary for decomposition and resembles an aryl cation. The intermediate X returns predominantly to $ArN^{+}{\equiv}N$ in such a way that both the nitrogen atoms become non-equivalent and kinetic isotope effect of 1.019 (in $N^{14}—N^{15}$) is indicative of C—N bond weakening. The intermediate Y is a more selective and less reactive species as its specific rate of return from Y to diazonium ion is nearly twice that of the isotopic rearrangement ($K_{SCN^-}/K_{H_2O}=4.70$) suggesting the equivalence of both the nitrogen atoms. A spiro cyclic structure is proposed for the intermediate Y.



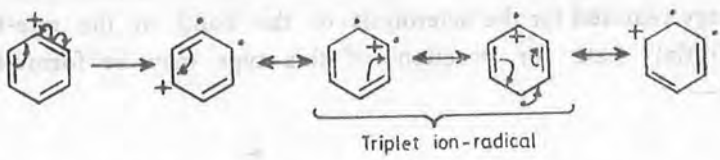
The selectivity of the intermediate is due to the stability of the aryl cation (Y) requiring greater participation of the aromatic electrons. The distance between the diazo nitrogen and the aromatic carbon to which it is linked is much shorter in the intermediate and hence greater positive charge is introduced into the aromatic ring.



In other words the intermediate Y closely resembles a benzenium ion and is thermodynamically more stable than the intermediate X because of the difference in their transient stability and is evidenced by the ratio of the rate constant of $S\bar{C}N$ and H_2O with benzenediazonium salt.

The rareness of aromatic SN_1 reaction is due to the absence of structural features which stabilize the aryl cation and stronger bonding in aromatic compound by the leaving group. The intermediate aryl cation can have a

triplet ion-radical character and thus gains some extra stability which would appear in the transition state.



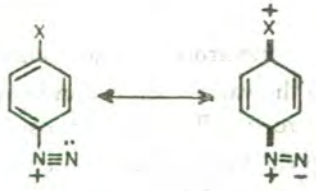
In triplet ion-radical a π electron of the benzene ring has entered with concerted uncoupling into the vacant sp-σ bond-orbital formerly occupied by the C—N bond electrons. The decomposition of benzenediazonium chloride in water has been shown to follow first order kinetics uneffected by the concentration or identity of the anion accompanying the diazonium cation and that the rate of phenol production is almost the same in D_2O and H_2O. The kinetic effect of substituents on the aromatic ring is characteristic and can readily be understood on the basis of unimolecular mechanism. Electron-releasing substituents at ortho and meta position of the diazonium ion facilitate the reaction while electron-withdrawing substituents at these positions retard the reaction. Electron-attracting para substituents retard the reaction but electron-donating para substituents are no more effective (Table 2).

TABLE 2

Rate of Decomposition of Benzenediazonium Salts in Water at 28.8°

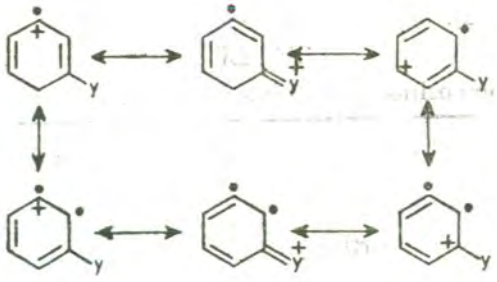
Substituents	$K1 \times 107.\ sec^{-1}.$		
	ortho	meta	para
—H	1	1	1
$-CH_3$	5.0	4.6	0.12
$-C_6H_5$	1.5	2.3	0.050
—OH	0.0092	12	0.0013
—Cl	0.0019	0.042	0.0019
$-NO_2$	0.0050	0.0093	0.0042
$-CO_2H$	0.19	0.55	0.12
$-SO_3^{2-}$	0.12	0.21	0.057

This is because electron-releasing groups at para position increase the double bond character by virtue of mesomeric effect strengthening the C—N bond as compared to the ortho substituents and increase the activation energy required for the heterolysis of the bond in the rate-limiting step. Initial state for reaction of this type may be formulated as follows :—



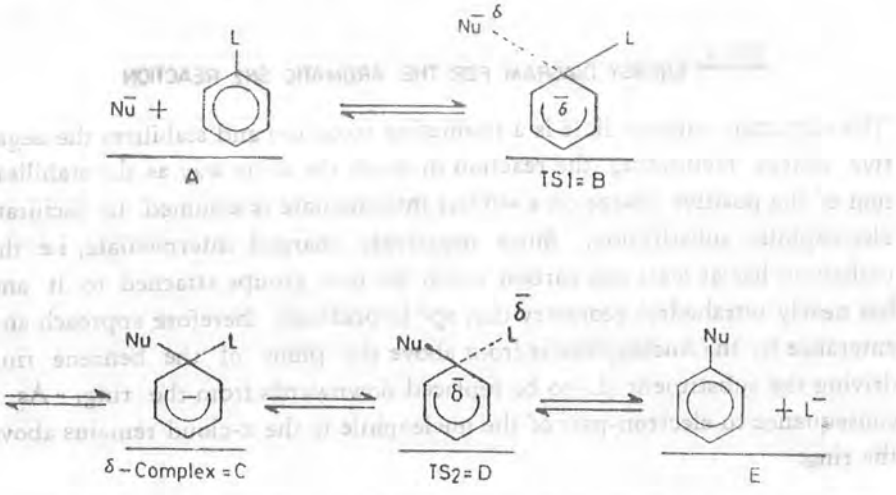
X = – OR , Ph , NH_2 , NHR , NR_2 , NHCOR , OCOR , F , Cl , Br , I , –CH=CH–CO_2H

The electron-releasing meta substituents facilitate the reactfon more strongly than would be expected because of the conjugation which would result stability of the aryl cation.



AROMATIC BIMOLECULAR SUBSTITUTIONS (ADDITION-ELIMINATION MECHANISM)

A typical nucleophilic aromatic substitution reaction is believed to involve an addition-elimination mechanism of SN_2 type in which first step is the addition of the nucleophilic agent (Nu) to the aromatic ring giving a carbanion intermediate and the ring substituent (L) is then expelled with its bonding electron pair as anion :



According to the scheme C—L bond is not weakened in reaching first transition state (TS_1) but the energy is consumed in disrupting the aromatic character of the substance by altering the π-electron distribution in the aromatic ring. As a result geometry of the carbon atom under attack is changed from sp^2 hybridised state to near sp^3 hybridised state and a new sigma bond (C—Nu) is formed. The carbanion-type intermediate or a σ-complex formed is non-aromatic. However rearomatisation of the σ-electron sextet is restored after the second transition state (TS_2) by the explusion of the ring substituent (L) as anion. This is illustrated in an energy profile with solid line (Fig. 1).

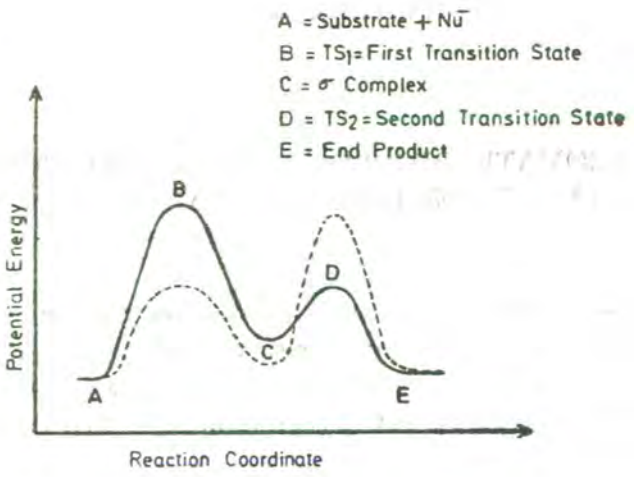
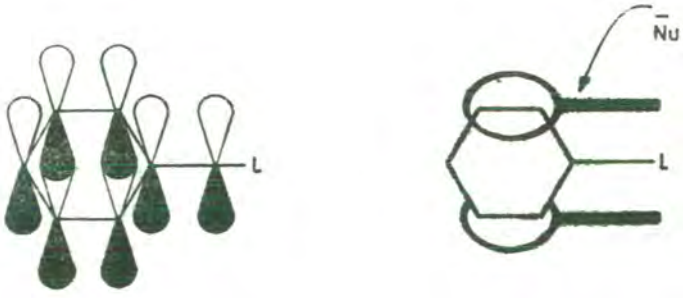


FIG. I. ENERGY DIAGRAM FOR THE AROMATIC SN2 REACTION

The carbanion intermediate is a resonating structure and stabilizes the negative charge facilitating the reaction in much the same way as the stabilisation of the positive charge on a similar intermediate is assumed to facilitate electrophilic substitution. Since negatively charged intermediate, i.e. the carbanion has at least one carbon which has four groups attached to it and has nearly tetrahedral geometry (i.e. sp^3 hybridized) therefore approach and enterance by the nucleophile is from above the plane of the benzene ring driving the substituent (L) to be replaced downwards from the ring. As a consequence to electron-pair of the nucleophile to the π-cloud remains above the ring.



The back-side attack would require the entering group (Nu) from within the benzene ring which is a stereochemical impossibility in this case.

The reactivity of the aryl halide towards SN_2 reactions is much slower than the corresponding reaction of alkyl halides. This is two fold :

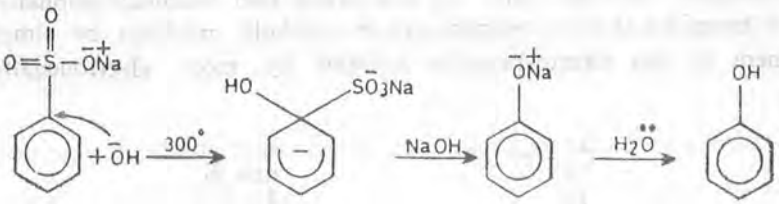
a. The energy required to disrupt the aromatic character of the substrate is too high under normal conditions.

b. The special character of the repulsive interactions between the π-electrons of the carbanion intermediate is present. This can very well be looked at the hydroxylation of chlorobenzene and substituted chlorobenzenes (Table 3).

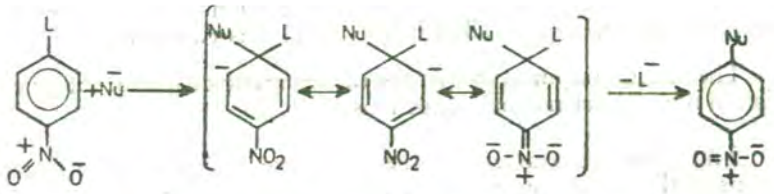
TABLE 3

SUBSTRATE	BASE	CONDITION	PRODUCT
Chlorobenzene	NaOH 8 %	350° &4500 lb/in^2	Phenol
4-Nitrochlorobenzene	NaOH 15 %	160°	4-Nitrophenol
2,4-Dinitrochlorobenzene	Na_2CO_3 aq.	130°	2,4-Dinitrophenol
2,4,6-Trinitrochlorobenzene	H_2O	warm	2,4,6-Trinitrophenol

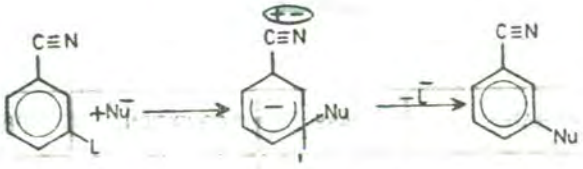
In these reactions the formation of phenol is dependent of the reaction conditions and the substrate involved. Hence for preparing phenol from chlorobenzene high temperature and pressure is required whereas similar phenols are prepared easily by putting suitable substituents on the aromatic substrate before hydroxylation thus indicating that the energy required for the reaction has been reduced to a greater extent and therefore the reaction can proceed under normal conditions. The cleavage of benzenesulphonate in alkaline medium is another example of high energy requirement for preparing phenols.



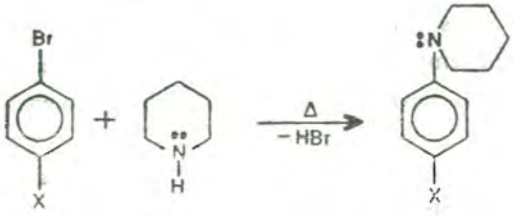
Bimolecular substitutions are encountered most frequently with substrates containing electron-withdrawing substituents of —M types. Such groups can stabilize the carbanion intermediate by resonance and disperse the negative charge brought in by the attacking nucleophile.



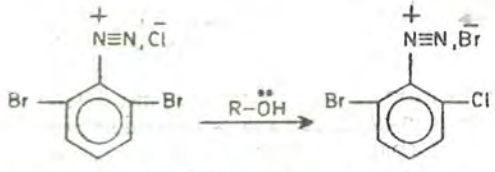
Group-dipoles of the electron-withdrawing substituents also facilitate rate of aromatic substitution.



The reactivity of halogenobenzene in SN_2 reaction is influenced by these groups substituted at ortho position because halogens withdraw electrons mainly from ortho carbon atoms by inductive effect and therefore the nucleophilic attack is facilitated on these carbons. Nitro groups strongly activate SN_2 reactions in the aromatic series than any other group with —M effect. For instance, in the para-substituted bromobenzenes the reaction with piperidine in benzene reveals the order $X=NO_2(1.0) > CH_3SO_2$ $(0.053) > —CN(0.031) > CH_3CO—(0.013)$.



The presence of diazonium groups show strong activating effect on the reactivity of aryl halides and thus 2, 4-dibromo- and 2, 6-dibromophenyldiazonium chloride salts are converted into bromochlorophenyldiazonium bromides at room temperature in alcoholic medium by simple displacement of less electro-negative bromine by more electronegative chlorine.



These exchange reaction sometime eliminate nitrogen.

In bimolecular displacements the breakage of the C—L bond is not significant. Ordinarily chloro substituted benzene should react more slowly with nucleophiles than the corresponding bromosubstituted compound because C—Cl bond is more difficult to break than C—Br bond.

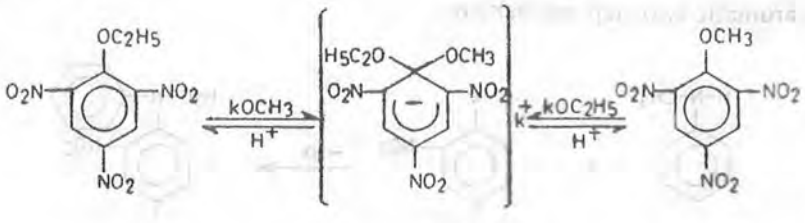
BOND TYPE	BOND DISSOCIATION ENERGY K Cals/mole.
C-Cl	82
C-Br	67

Experimentally it is observed that they react at almost the same rate and the activation energies for these reactions are nearly the same and independent of the substituent (L).

Kinetics of these reactions reveal that they are second-order processes :

$$\frac{d(P)}{dt} = k\,[ArL]\,[N\bar{u}]$$

The σ-complex formed in the reaction are isolable as stable salts containing the carbanion function. Thus it has been shown that potassium salt of 1-methoxy-1-ethoxy-2,4,6-trinitrobenzene anion is formed in two ways when the anion is stabilised by the delocalisation of the negative charge over the nitro groups.



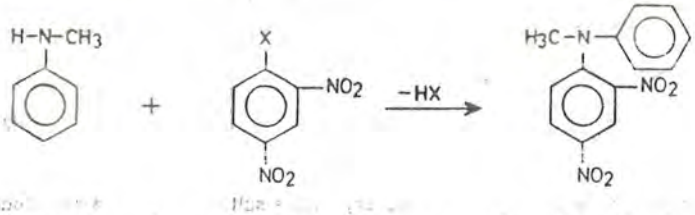
s-trinitrophenetole red crystalline salt s-trinitroanisole

Decomposition of the red salt in acid medium results mixture of both the trinitroanisole and trinitrophenetole. The infra red and visible spectrum of the salt prepared by the two methods separately are identical and are in accordance with the proposed structure of the intermediate. Picryl chloride gives a similar intermediate and so are the pyridine compound which produce coloured solutions.

where $R_1, R_2, R_3 = CH_3, NO_2, CN$ and $R_4 = Cl$ or $-OCH_3$

Kinetic studies reveal that aryl fluorides react faster than the corresponding aryl halides ($kArF > kArCl \simeq KAyBr \simeq KArI$) which is contrary to the SN_2 reactivities of alkyl halides. The reason is that the amount of fluorobenzene anion formed is larger than the other halobenzene anions in the first step (which is rate-determining) due to the larger stabilising polar effect of highly electronegative fluorine. In the second step, which is fast step, although fluorine is poor leaving group but its above mentioned properties become less significant in aromatic displacements.

It may be pointed out that the order of halogen displacement mentioned above for aromatic substitutions is usual one but for some reactions this order is reversed. For instance, in the reaction of N-methylaniline with 1-halogeno-2,4-dinitrobenzenes the observed order is $kArBr > kArCl > kArF$ and resembles that of aliphatic bimolecular nucleophilic substitution. On this basis. it can be argued that such reactions which obey SN_2 (aliphatic) order of reactivity proceed through a different mechanism than the usual SN_2 aromatic two step mechanism.

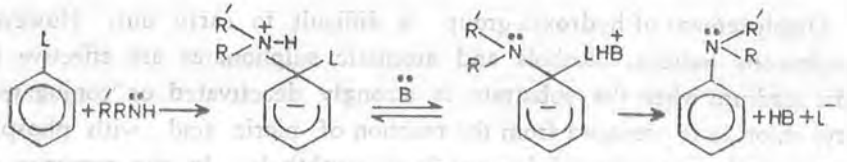


Reactions following the group displacement order $Br > Cl > F$ proceed through one step SN_2 mechanism and that the observed order is not inconsistant with the two-step SN_2 mechanism.

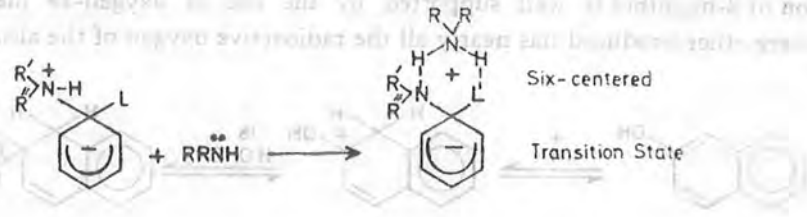
For example, if L is a good leaving group than y (when L=F and Y=Br) then K-1 > > K_2. K_2 shall be the rate determining step of the reaction anp K_2 shall be greater if L=Br than L=F. The rate of attack by different reagents on the same aryl halide follows the general order of nucleophilicity. For chloride ion displacement the rate-order of the nucleophilic agents is $\overline{O}C_2H_5 > \overline{O}Ph >$ piperidine > aniline > $\overline{I} > \overline{Br}$.

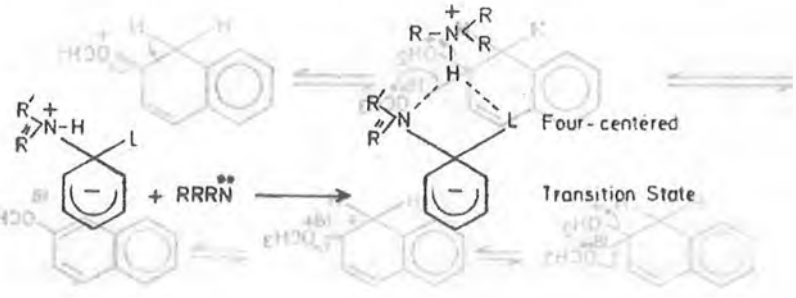
The base catalysed reactions become reversible when the leaving group (L) is relatively slow to expulsion such as —OMe or —OPh. The energy profile for these reactions is different (Fig. 1 dotted line) where the concentration of the σ-complex remains small during the reaction.

Mechanisms for the base catalysis are suggested to involve either the removal of the proton from the intermediate complex followed by acid



catalysis. or a multi-centered hydrogen bonded transition state for secondary or tertiary amine catalysis.



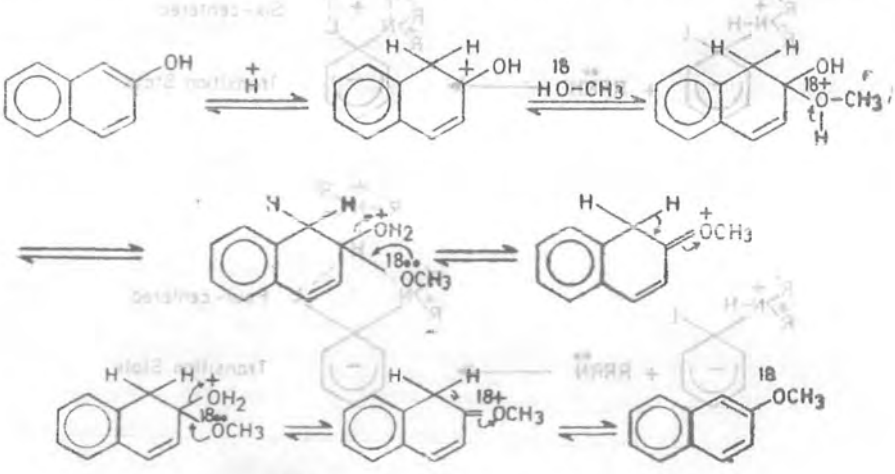


GROUP DISPLACEMENTS IN AROMATIC NUCLEOPHILIC SUBSTITUTIONS

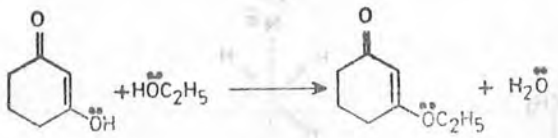
Most easily displaceable groups on the aromatic ring include, alkoxyl, hydroxyl, amino, nitro, sulphite and halides when the aromatic ring is activated by diazo, nitroso, nitro, trialkylammonium and alkylsulphonate groups.

(a) *Displacement of Hydtoxyl, Alkoxpl and Aryloxyl Gronps*

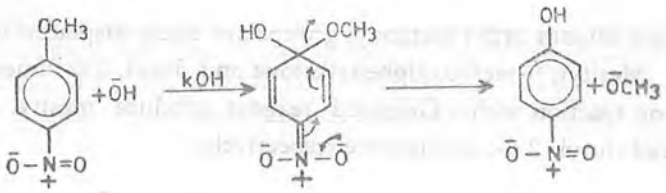
Displpcement of hydroxyl group is difficult to carry out. However phosphorous halides, alcohols and aromatic sulphonates are effective in acidic medium when the substrate is strongly deactivated or conjugated. Picryl chloride is prepared from the reaction of picric acid with phosphorous chloride and halonaphthalenes from naphthols. In the presence of acids (in alcoholic solvents; ethers are produced. Thus resorcinol, phloroglucinol and naphthols result in ethers. The mechanism of the etherification of β-naphthol is well supported by the use of oxygen-18 methanol where ether produced has nearly all the radioactive oxygen of the alcohol.



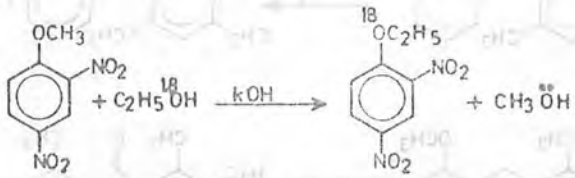
Dihydroresorcinol in ethanol and p-toluenesulphonic acid give 3-ethoxycyclohexanone-2 by a similar mechanism :



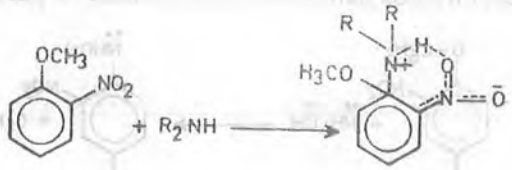
Alkoxyl groups are displaced from the activated aromatic nucleus with strong alkali in which the electronegative group accommodates negative charge and help in displacement of the alkoxyl group.



The rupture of the aryl-oxygen bond is demonstrated by the reacti on of 2,5-dinitroanisole with ^{18}O-labelled ethanol yielding the labelled phenetole.

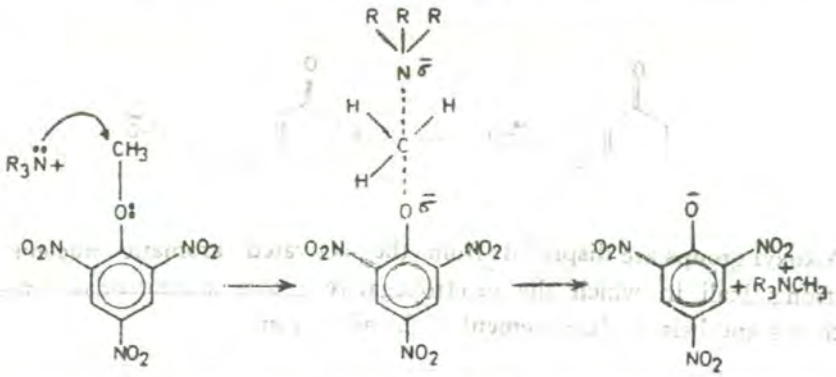


Primary or secondary amines and nitro anisole form Meisenheimer complexes and intramolecular hydrogen bonding between the N-H and the ortho nitro group.

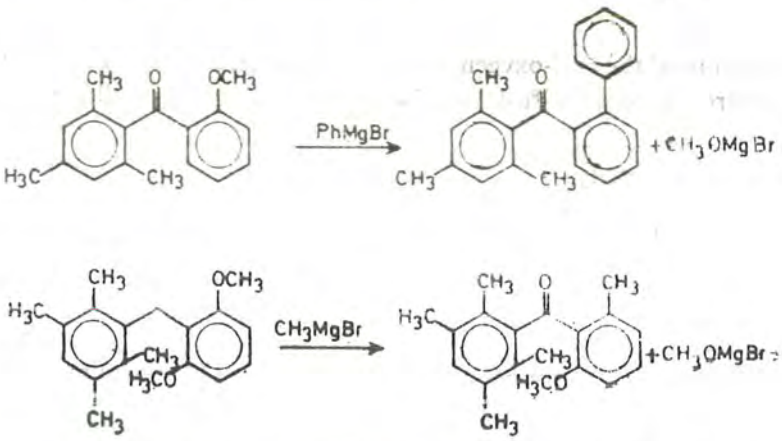


Whereas tertiary amines have no possibility for intramolecular hydrogen bonding with the ortho nitro substituent. Therefore attack occurs on the

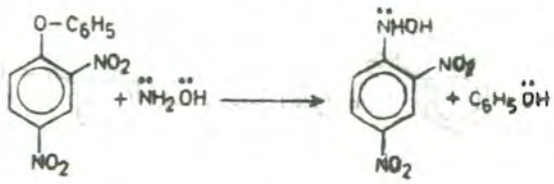
methyl-oxygen bond by an aliphatic bimolecular nucleophilic substitution reaction leading to the formation of quaternary ammonium salts.



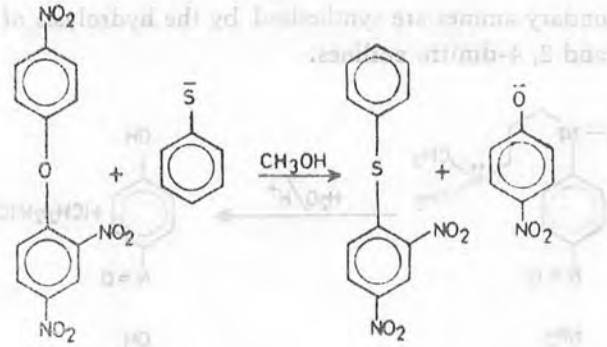
In hindered ketones ortho methoxyl groups are easily displaced by Grignard reagent. Mesityl, 0-methoxylphenylketone and duryl, 2,6-dimethoxylphenylketone on reaction with a Grignard reagent produce mesity, 2-biphenylketone and duryl, 2,6-, xylylketone respectively.



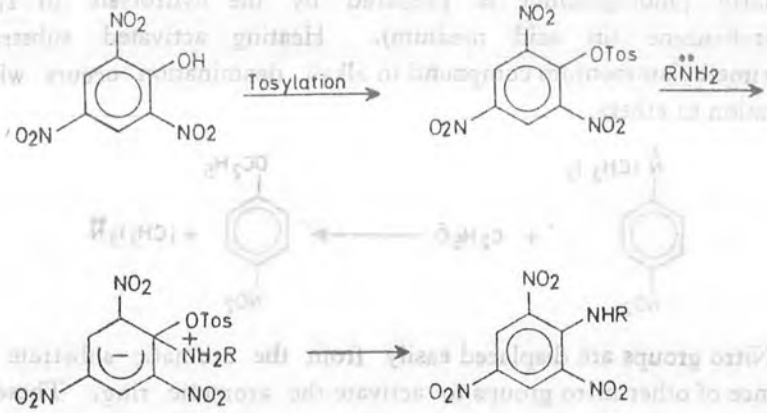
Reaction of hydroxylamine with phenyl ether of 2,4-dinitrophenol result 2,4-dinitrophenyl hydroxylamine by displacement of phenoxide ion.



Similarly mercaptides replace aryloxy group from the substrate.

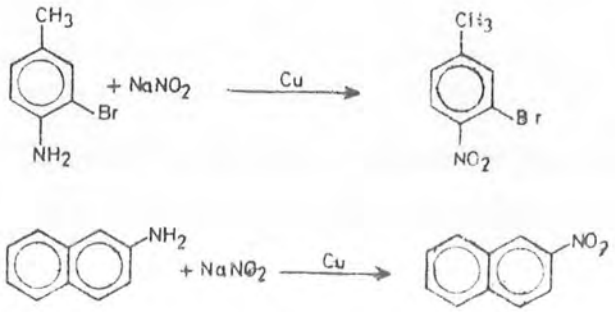


An indirect displacement of hydroxyl group from nitrophenols is achieved by tosylation in which strong electron-withdrawing effect of the sulphonyl function makes the tosylate a good leaving group when reacted with amines.

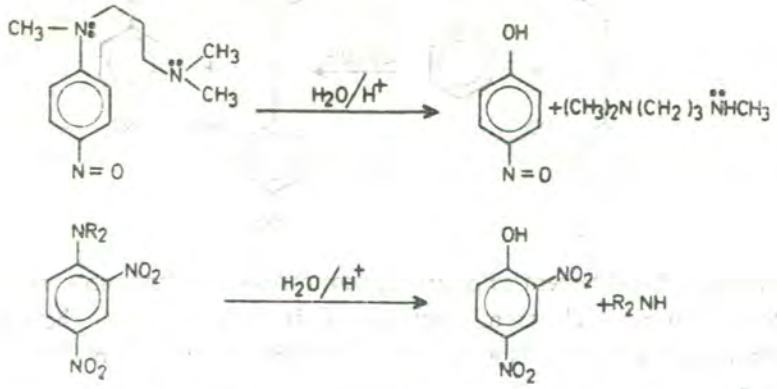


(b) *Displacement of Amino and Nitro Groups*

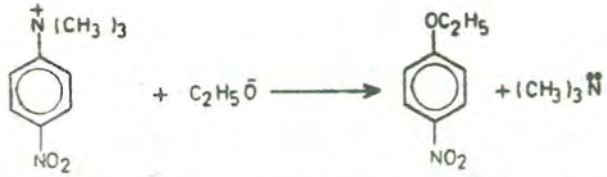
Nitrobenzenes and nitronaphthalenes are prepared from the corresponding amino benzenes or naphthalenes when treated with sodium nitrite in the presence of copper catalyst.



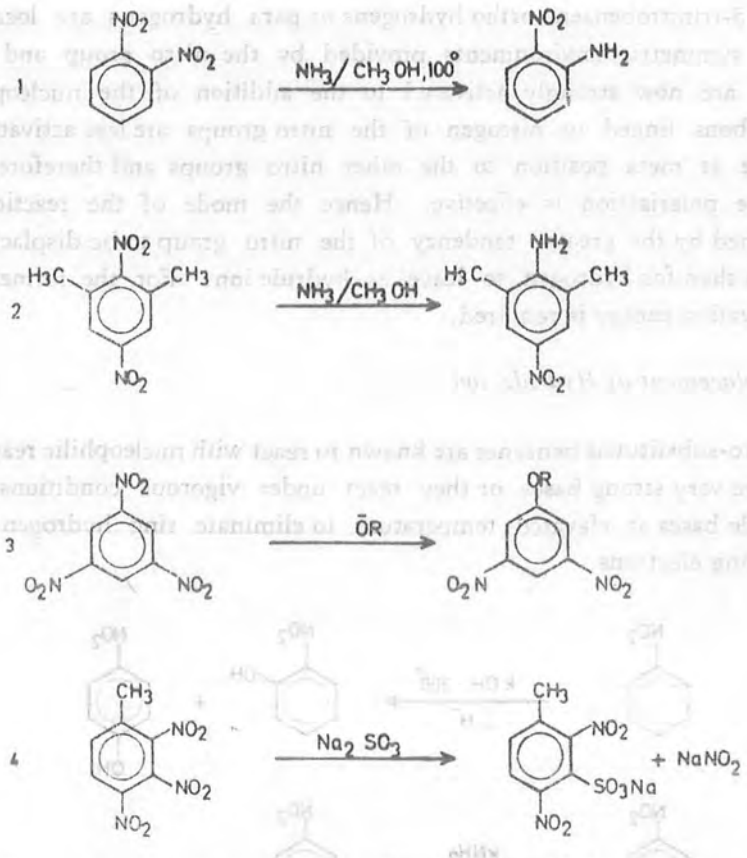
Pure secondary amines are synthesised by the hydrolysis of p-nitrosodialkyl anilines and 2, 4-dinitro anilines.



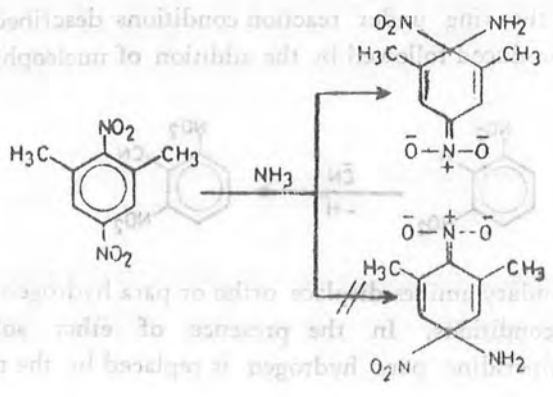
Similarly phloroglucinol is prepared by the hydrolysis of 1, 3, 5-trinitrobenzene (in acid medium). Heating activated substrate of aryltrimethylammonium compound in alkali, deamination occurs with the formation of ethers.



Nitro groups are displaced easily from the aromatic substrate in the presence of other nitro groups to activate the aromatic ring. These nitro groups may be at ortho, at para or at meta to the displaceable nitro group. The displacements are effected by alkali, alcoholic ammonia, alkoxide ions or sodium sulphite.



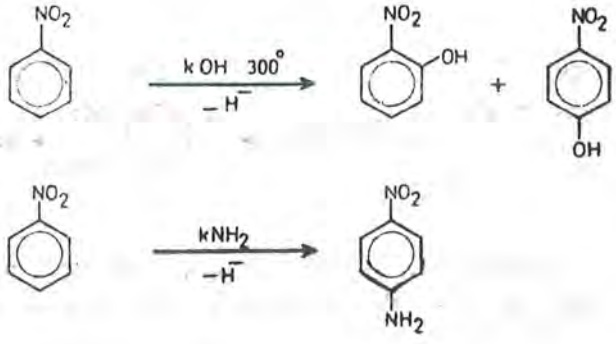
In substrate containing 1, 4-nitro groups, hindered nitro group. reacts at a faster rate than the unhindered nitro group. The steric hinderance offered by bulky methyl group forces the nitro group to become non-coplanar with the benzene ring.



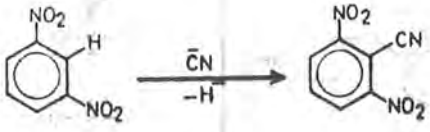
In 1, 3, 5-trinitrobenzene ortho hydrogens or para hydrogens are localised due to symmetric environments provided by the nitro group and these carbons are now strongly activated to the addition of the nucleophile. But carbons linked to nitrogen of the nitro groups are less activated as they are at meta position to the other nitro groups and therefore only inductive polarisation is effective. Hence the mode of the reaction is determined by the greater tendency of the nitro group to be displaced as NO_2 ion than for hydrogen to leave as hydride ion. For the former ion less activation energy is required.

c. *Displacement of Hydride ion*

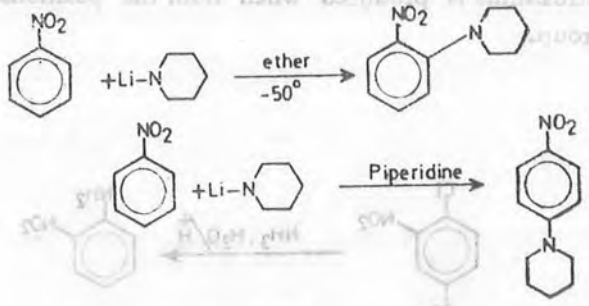
Nitro-substituted benzenes are known to react with nucleophilic reagents which are very strong bases or they react under vigorous conditions with hydroxide bases at elavated temperature to eliminate ring hydrogen with its bonding electrons.



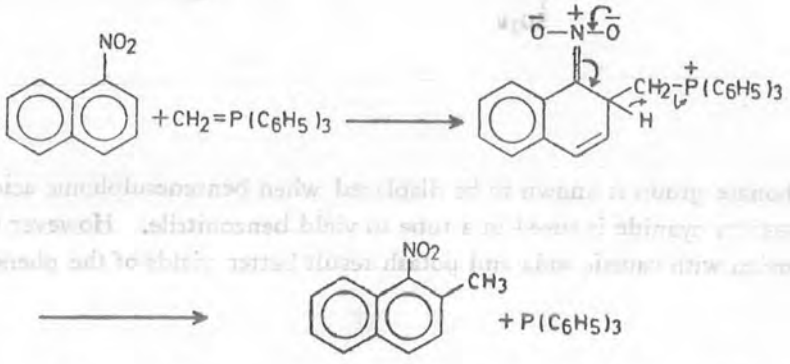
The presence of second nitro group at meta position on the substrate strongly activate the ring under reaction conditions described above and hydride ions are produced followed by the addition of nucleophile.



Metal salts of secondary amines displace ortho or para hydrogen depending on the reaction conditions. In the presence of ether solvent ortho hydrogen and in piperidine para hydrogen is replaced by the metal amine salt.



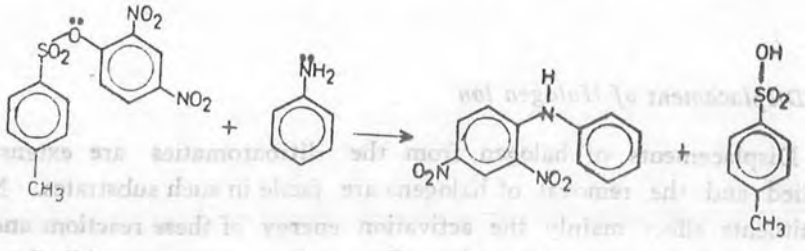
Ylids are known to displace nucleophilic hydrogen and introduce a methyl group in the ring.



These nucleophilic displacements are not common and their use in organic synthetic chemistry is very limited.

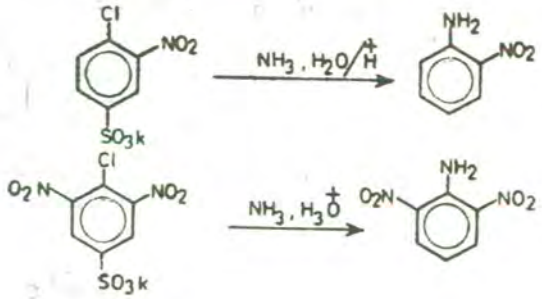
d. *Displacement of sulphonates*

Aromatic secondary amine can be prepared from the reaction of tosylesters of 2, 4-dinitrophenol and aniline by displacing sulphonate group.

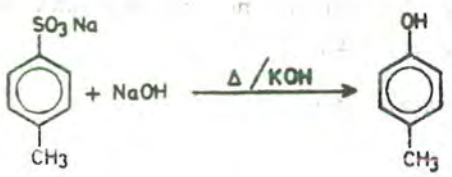


Nitroanilines are prepared from chlorobenzene by making use of a sulphonate group as a blocking agent at para position with respect to the chloro substituent. A nitro group at 2-or 6-position gives o-nitroaniline

while 2, 6-dinitroaniline is produced when both the positions are blocked by the nitro group.

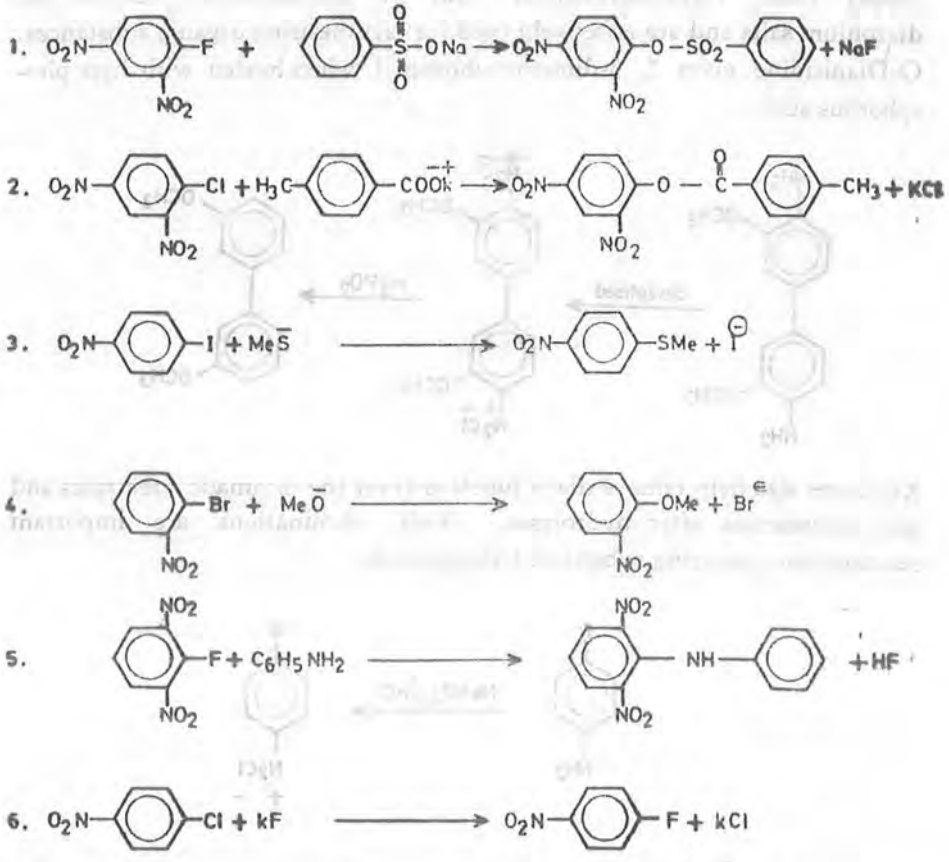


Sulphonate group is known to be displaced when benzenesulphonic acid and potasssium cyanide is fused in a tube to yield benzonitrile. However tosyls on fusion with caustic soda and potash result better yields of the phenols.



e. *Displacement of Halogen ion*

Displacements of halogen from the ditroaromatics are extensively studied and the removal of halogens are facile in such substrates. Nitro subsituents effect mainly the activation energy of these reactions and are ortho-para activating ; the ortho effect being stronger. All the four halides are displaced easily from ortho or ortho-para disubstituted substrate by sulphite. carboxylate, sulphide, alkoxy, amino groups and by halogen exchange reactions in polar solvents.

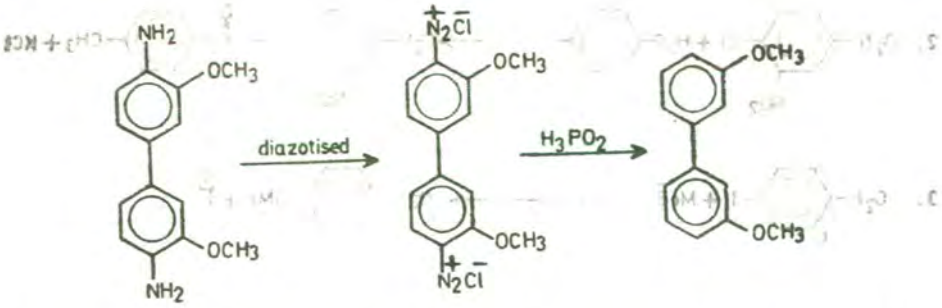


Mercaptides and alkali bases displace chloride, fluoride and bromide ; azides and thiocyanate ions remove fluoride and iodide while carbanions replace chloride and fluoride in the nucleophilic aromatic displacement reactions. However chloride ion is also replaced by sodium iodide, xanthates, amides, bromide in the presence of copper catalyst and by ammonia under high temperature and pressure.

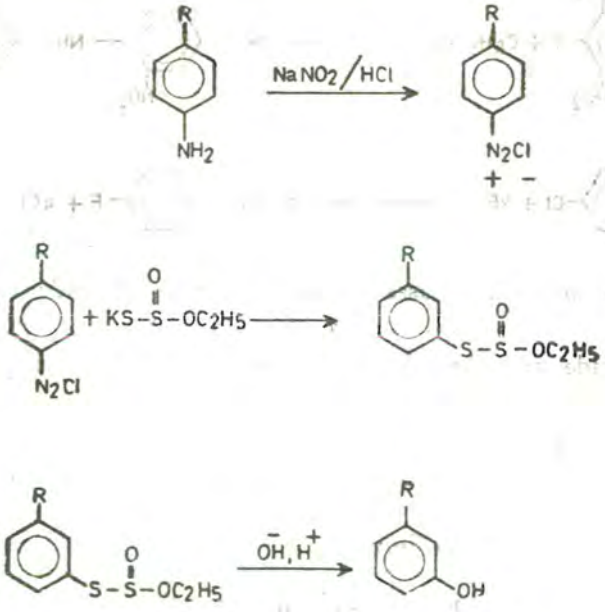
f. *Displacement of Diazo Group*

Halogens such as iodine and fluorine displace diazo group from aromatic diazonium salts and give halobenzenes in good yield. Aquous solutions of these salts result phenols in acidic solutions. The rate of the decomposition of the diazo compound varies with the ring substituent present, such as chloro, alkoxyl or nitro groups. Alcohols also result similar displacements. These reactions are accelerated when catalysed by

copper ions. Hypophosphorous acid or formaldehyde reduces the diazonium salts and are effectively used for synthesising organic substances. O-Dianisidine gives 3, 3-dimethoxybiphenyl when heated with hypophosphorous acid.



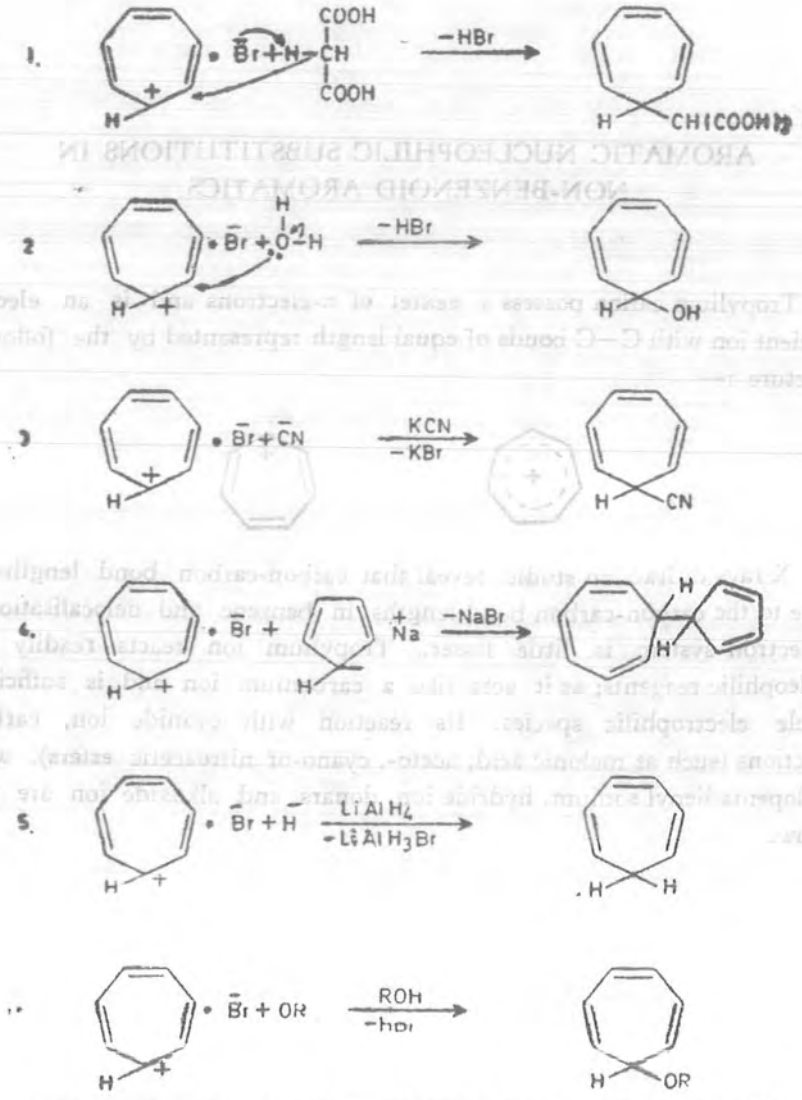
Xanthates also help remove diazo function from the aromatic substrates and give thiophenols after hydrolysis. Such eliminations are important reactions for preparing substituted thiophenols.



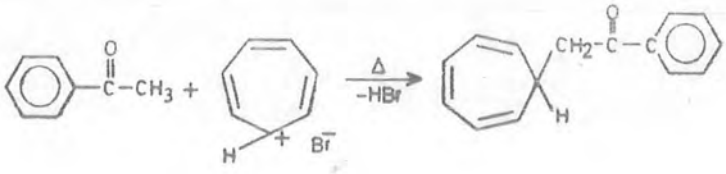
AROMATIC NUCLEOPHILIC SUBSTITUTIONS IN NON-BENZENOID AROMATICS

Tropylium cation possess a sextet of π-electrons and is an electron deficient ion with C—C bonds of equal length represented by the following structure :—

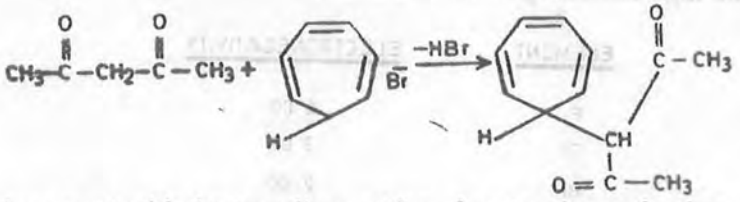
X-rays diffraction studies reveal that carbon-carbon bond lengths are close to the carbon-carbon bond lengths in benzene and delocalisation via π-electron system is little lesser. Tropylium ion reacts readily with nucleophilic reagents; as it acts like a carbonium ion and is sufficiently stable electrophilic species. Its reaction with cyanide ion, carboxyl functions (such as malonic acid, aceto-, cyano-or nitroacetic esters), water, cyclopentadienyl sodium, hydride ion donars and alkoxide ion are given below.



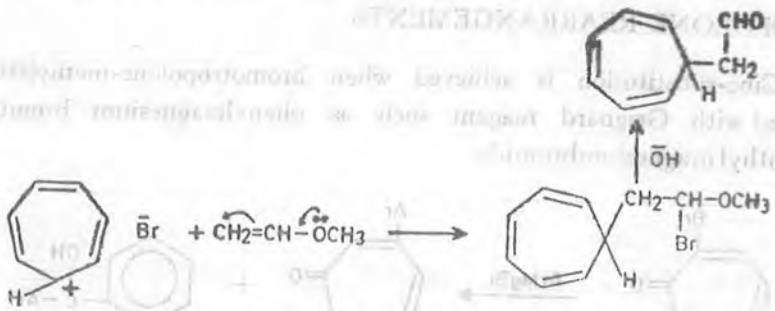
Monoketones in the absence of activating groups are tropylated under stringent conditions requiring reflux for a longer time and as a result α-hydrogen from an alkyl group is replaced giving a carbanion which then attacks the tropylium cation.



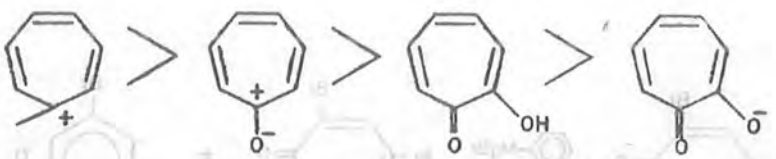
In the presence of an activating group ketones readily react with tropylium salts at room temperature.



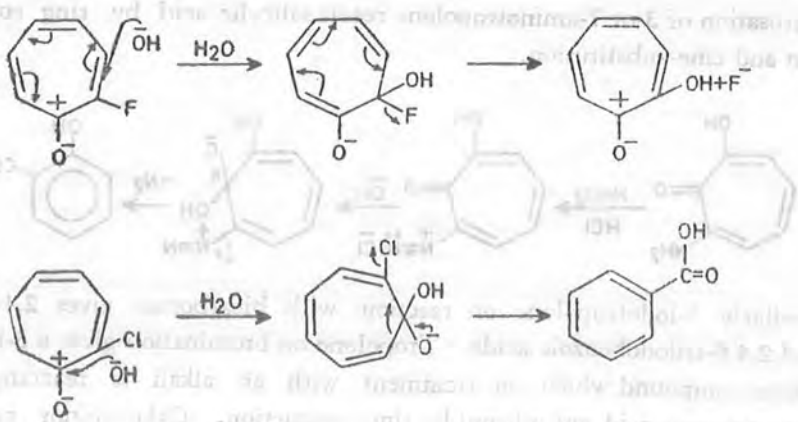
Vinyl ethers react with the tropylium cation due to the activation of the double bond by the electronegative oxygen present in the vicinity.



The electrophilic reactivity of tropylium cation, tropone, tropolone and tropolonate anion respectively towards nucleophiles is in the order of



2-Fluorotropone and 2-chlorotropone on hydrolysis yield tropone and benzoic acid, former reaction occurs by normal subtitution at 2-position while the later reaction involves ring contraction and attack by the nucleophile at 1-position.

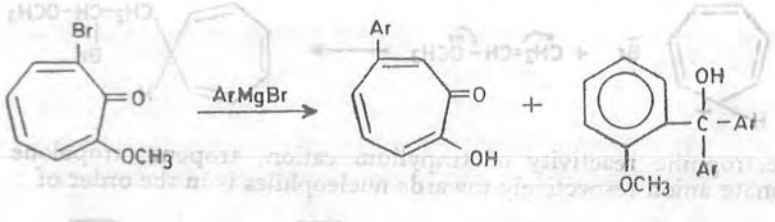


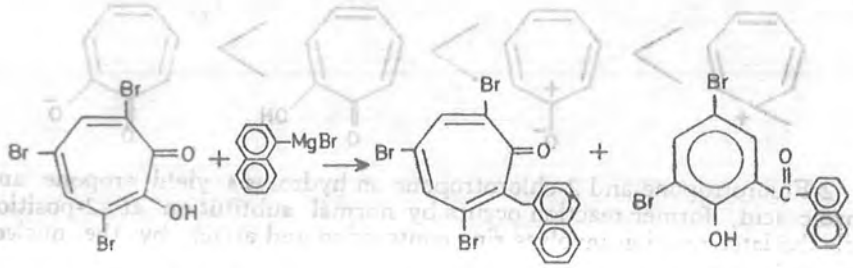
The nucleophilic attack at different position for fluoro and chlorotropone is due to the high electronegativity of fluorine as compared to chlorine.

ELEMENT	ELECTRONEGATIVITY
F	4·00
Cl	3·00
Br	2·00
I	2·50

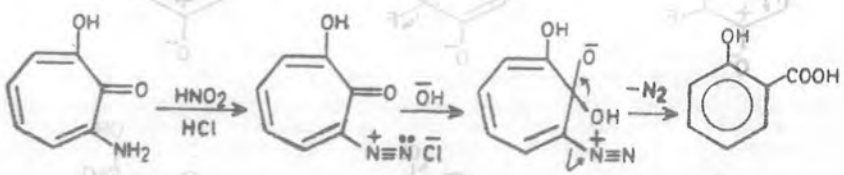
TROPOLONE REARRANGEMENTS

Cine-substitution is achieved when bromotropolone-methylether is treated with Grignard reagent such as phenylmagnesium bromide or naphthylmagnesiumbromide.



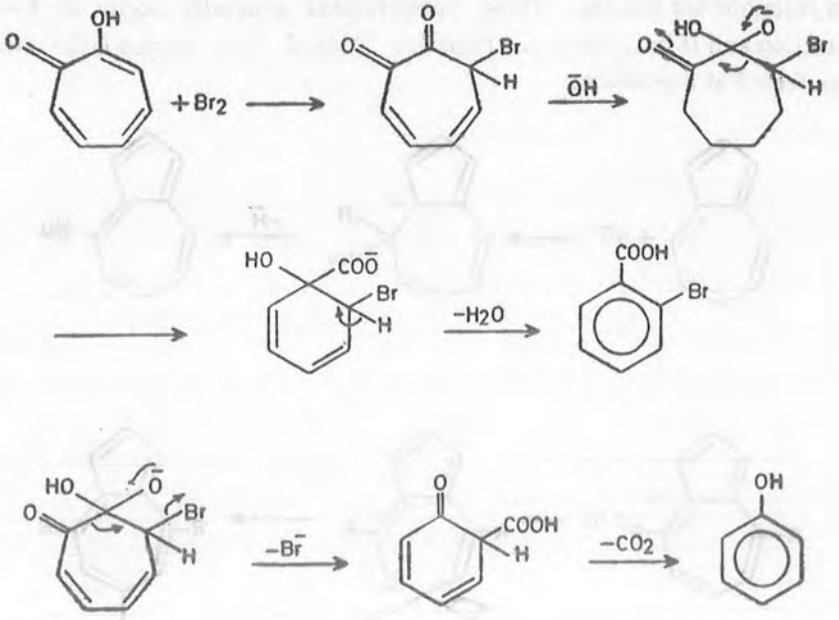


Nitrosation of 3-or 7-aminotropolone result salicylic acid by ring contraction and cine-substitution.

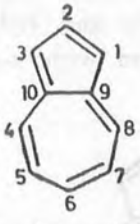


Similarly 3-iodotropolone on reaction with bicarbonate gives 2,4-diiodo and 2,4,6-triiodobenzoic acids. Tropolone on bromination gives a 3-bromo-diketo-compound which on treatment with an alkali is rearranged to bromobenzoic acid and phenol by ring contraction. Other minor products

are also formed in which ring is not contracted but bromine is substituted on t ropolone.



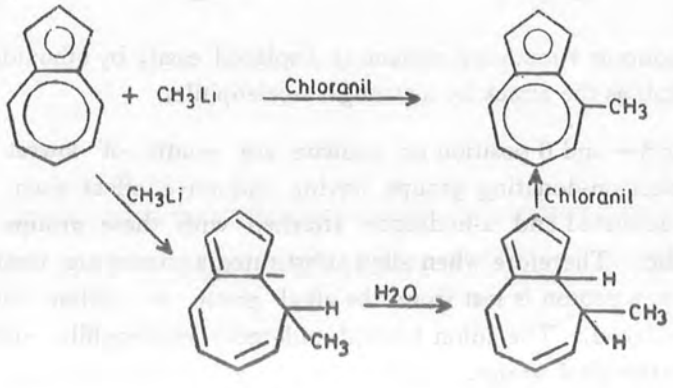
Azulene show the decreasing ease of attack by a nucleophile at various carbons in the following order :



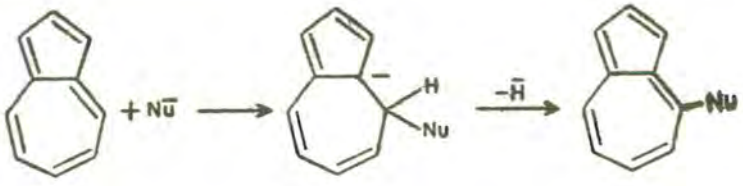
4 > 6 > 5 > 2 > 1

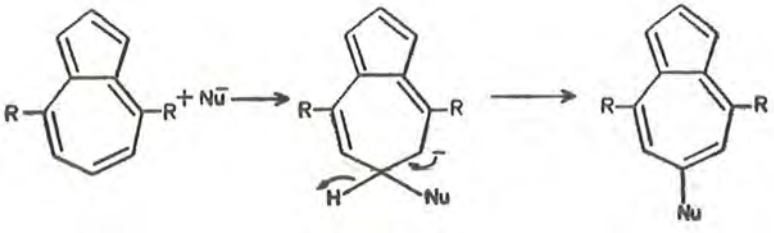
4 or 8 > 6 > 5 or 7 > 2 > 1 or 3

Metal alkyls give substitutions reaction at 4- or 8-position and hydride ions are expelled in the presence of chloranil which acts as a dehydrogenating agent.

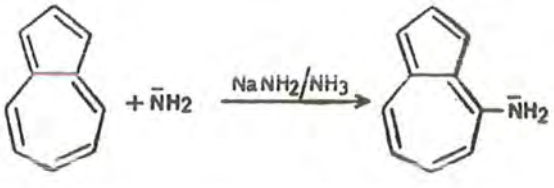


Due to instability of azulene towards bases very few nucleophilic substitution reactions are known. These substitutions generally occur at 4— or 8-position and if both these positions are blocked then nucleophilic attack is preferred at 6-position.



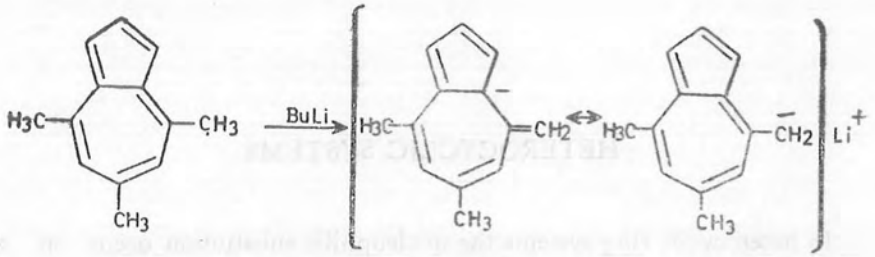


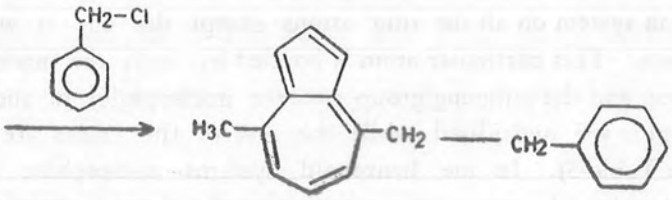
Sodamide in liquid ammonia on reaction with azulene gives 4-aminoazulene, which is a basic compound and somewhat unstable and red in colour because of conjugation of the azulene aromatic system with π-electrons of the nitrogen.



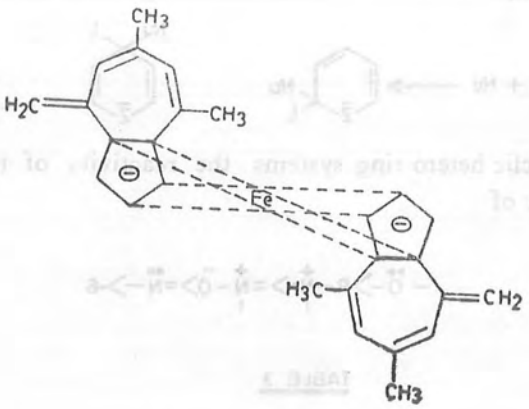
Methoxy group in 4-methoxy azulene is displaced easily by ethoxide ion or a strong alkali as the attack by a stronger nucleophile.

Since 4— or 8— and 6 position on azulene are points of lowest density therefore electron-donating groups having inductive effect such as alkyl groups are activated and α-hydrogen attached with these groups become weakly acidic. Therefore when alkyl substituted azulenes are treated with strong bases, a proton is lost from the alkyl group or carbon chain and anion is produced. The anion formed undergoes electrophilic substitution reactions at the alkyl group.





The carbanion formed above is also known to react with $FeCl_3$ to form a ferrocene-like compound.



HETEROCYCLIC SYSTEMS

In heterocyclic ring systems the nucleophilic substiution occur on the ring carbon atoms due to the ability of the hetero-atom to stabilize the aromatic character of the intermediate complex by redistributing the charge over the π-electron system on all the ring atoms except the one at which substitution occurs. This particular atom is bonded by both the incoming nucleophilic group and the outgoing group (weaker nucleophile) in such a way that the atom is sp^3 hydridised while the rest of the atoms are sp^2 hydridised (see Table-3). In the benzenoid systems nucleophilic substitution generally takes place at α— or γ-position to the hetero atom than at the β-position because negative charge produced in the intermediate complex can be delocalised on the hetero atom which is more electronegative than carbon.

In monocyclic hetero ring systems the reactivity of the hetero-atoms are in the order of

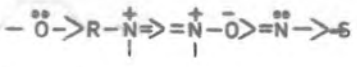


TABLE 3

ELEMENT	SYMBOL	ELECTRONEGATIVITY	CONFIGURATION OF VALENCE ELECTRON
Carbon	C	2.5	$2S^2$, 2PX, 2PY
Oxygen	O	3.5	$2S^2$, 2PX, 2PY, 2PZ
Nitrogen	N	3.0	$2S^2$, 2PX, 2PY, 2PZ
Sulphur	S	2.5	$3S^2$, 3PX, 3PY, 3PZ

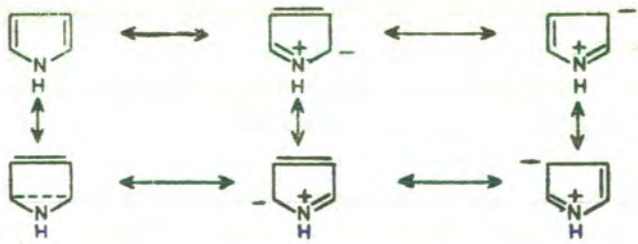
In five-membered heterocyclic rings, the negative charge produced in the intermediate complex lies on the carbon next to the hetero atom for ubsstitution at α-position (see resonance contributing structures)

The σ-inductive effect of the hetero-atom increases the electronegativity of the neighbouring carbon and the negative charge of the arenide system is placed there. Most of these substitutions are bimolecular in nature and are activated by electron-withdrawing groups which are capable of stabilising or destabilising the intermediate camplex.

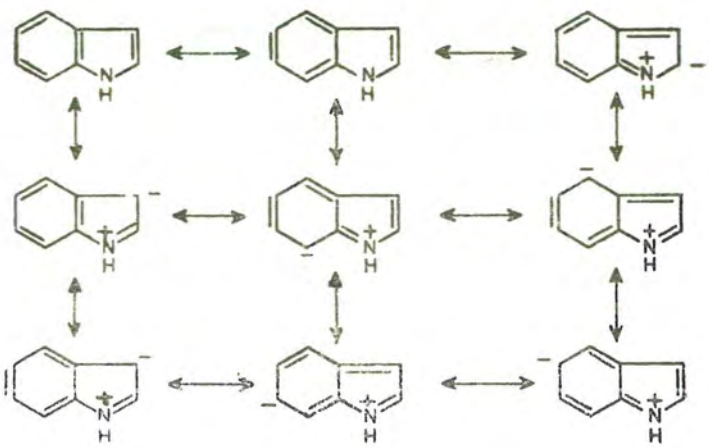
Since heterocyclic systems are well known bases of varied strength therefore the substitutions by the nucleophilic reagents which are generally basic in nature sometime are carried out by proper reaction control. Thus with basic nucleophilic reagents acids are added to activate the reaction and with strong bases neutral reagents are generally used in the reaction mixture containing heterocyclic species.

RESONANCE CONTRIBUTING STRUCTURES

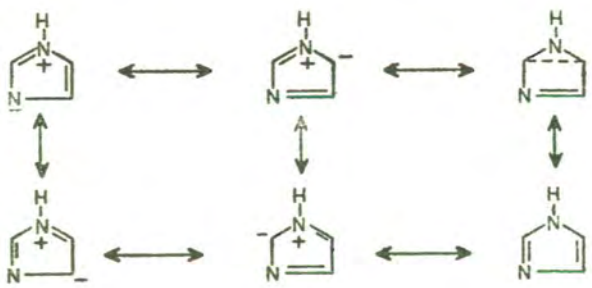
PYRROLE



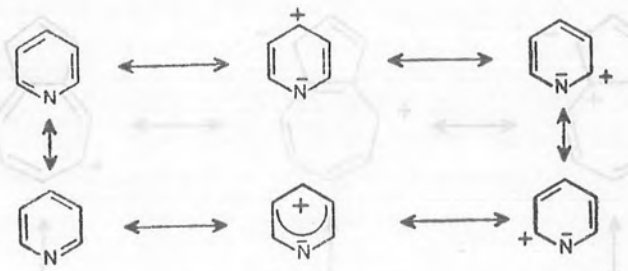
INDOLE



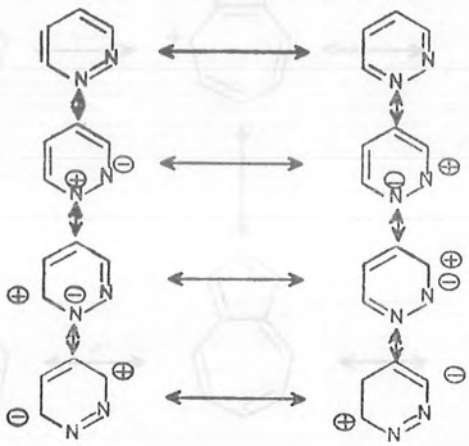
IMIDAZOLE



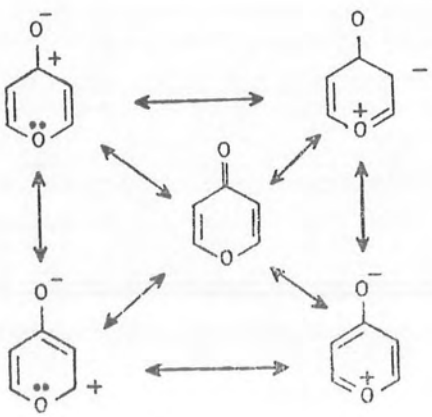
PYRIDINE



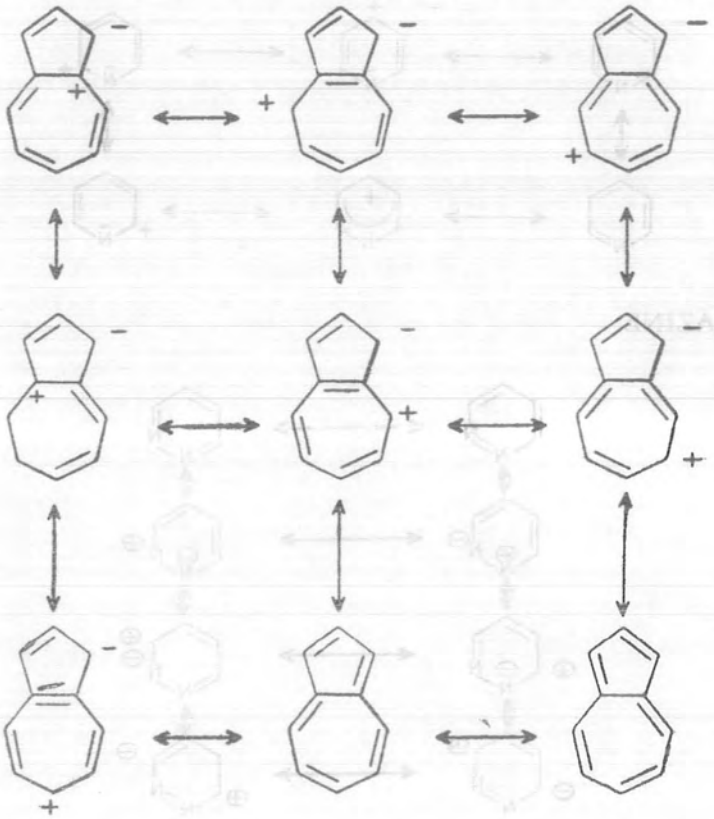
PYRIDAZINE



α-PYRONE

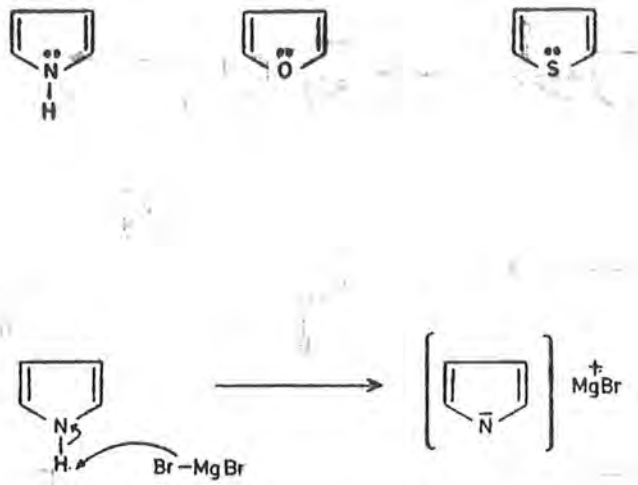


AZULENE



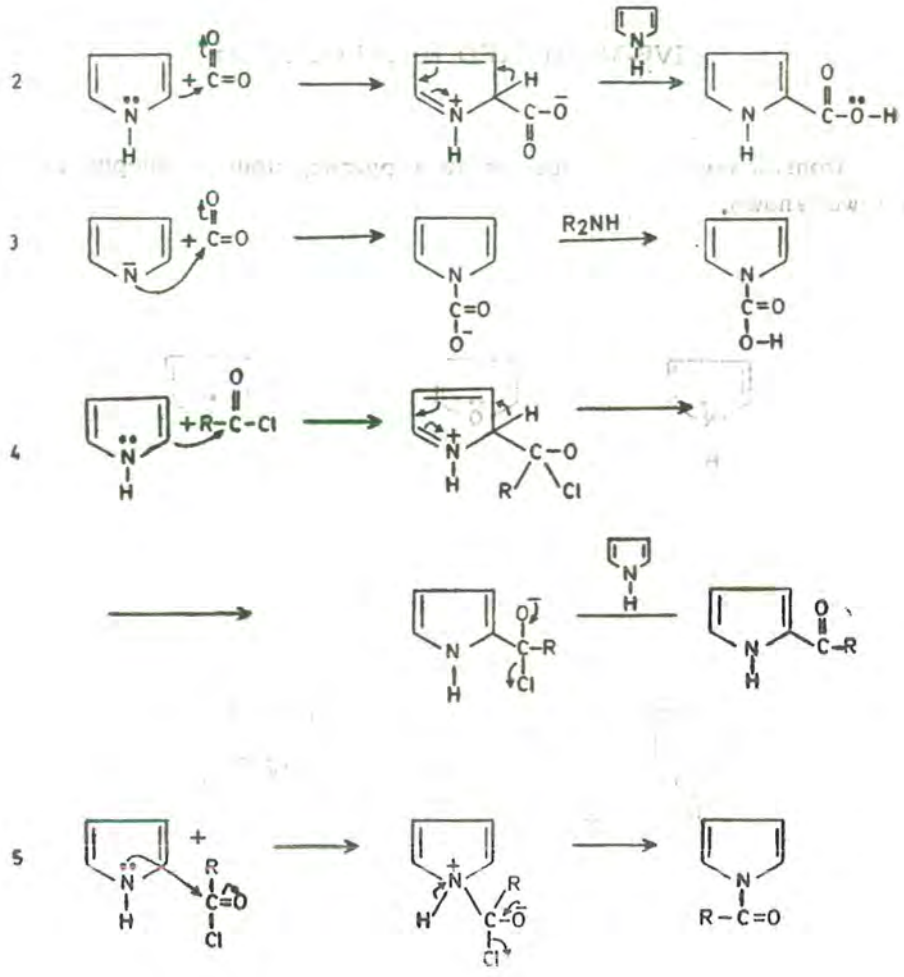
FIVE-MEMBERED HETEROCYCLES

Aromatic nucleophilic substitutions of pyrrole, furan or thiophene are not well known.

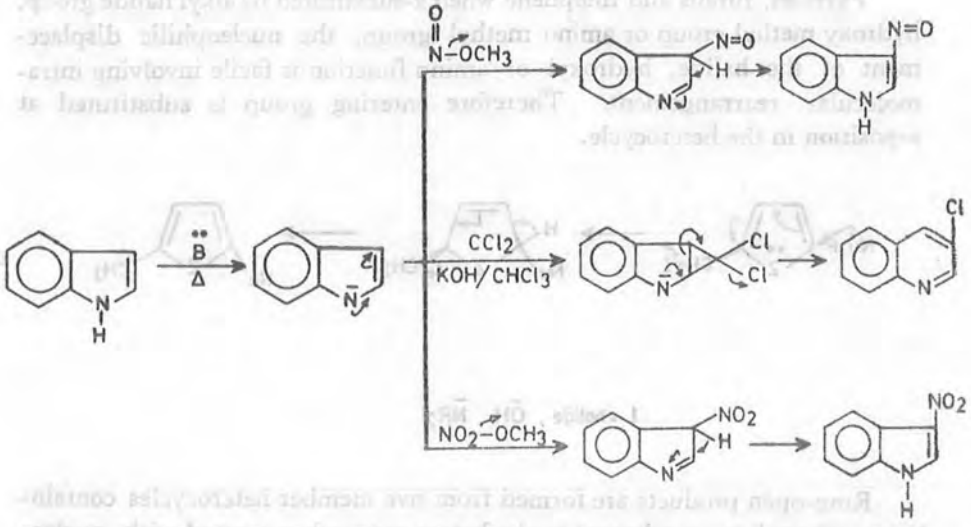


The NH group in pyrrole is acidic because electron pair on nitrogen can be delocalised on the ring carbons by resonance and makes the ring nitrogen less basic. Therefore the active hydrogen on the nitrogen is removed by Grignard reagent resulting in an ionic salt.

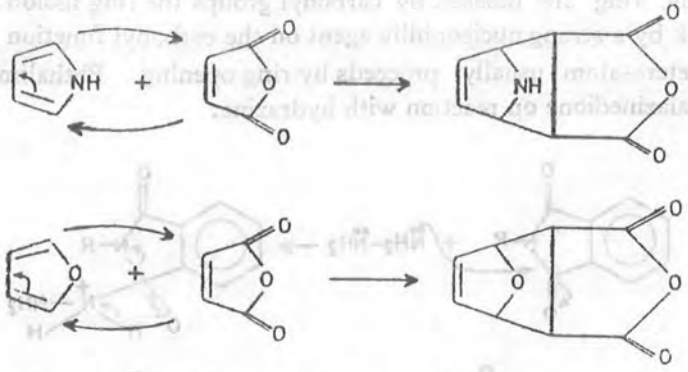
Pyrrole by virtue of being acidic can act as a nucleophile and thus its reaction with electrophilic reagents like halides give 2-alkylpyrrole ; while carbon dioxide, esters and acid chlorides result in 1-and 2-substitution products.



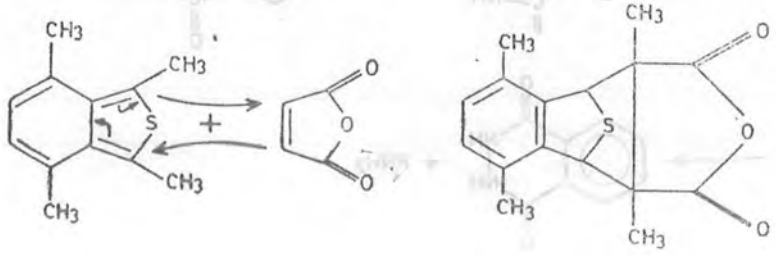
Pyrrole gives Grignard reagents when treated with alkali metalamides. These derivatives are mainly N-substituted as discussed before. However, when less basic reagents are used and the reaction mixture is heated then ring substitutions are predominant. Thus, the anion produced acts as nucleophile and give reaction with other electrophilic reagents such as alkyl nitrites, alkyl nitrates and with electron deficient species "carbenes".



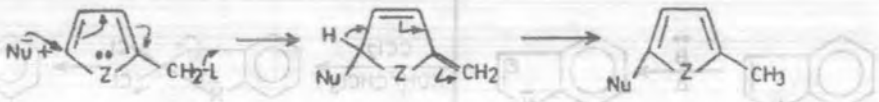
Furan and thiophene on reaction with Grignard reagents are ring metalated at 2-position. Pyrrole and furans have low resonance energy and possess diene character. As a result they undergo Diels-Alder reaction with dienophiles such as acid anhydride.



When five-membered heterocycles are 3, 4-benzo-substituted, extended conjugation in the molecules of isoindole, isobenzofuran and isothionaphthene show reactivity towards dienophiles.

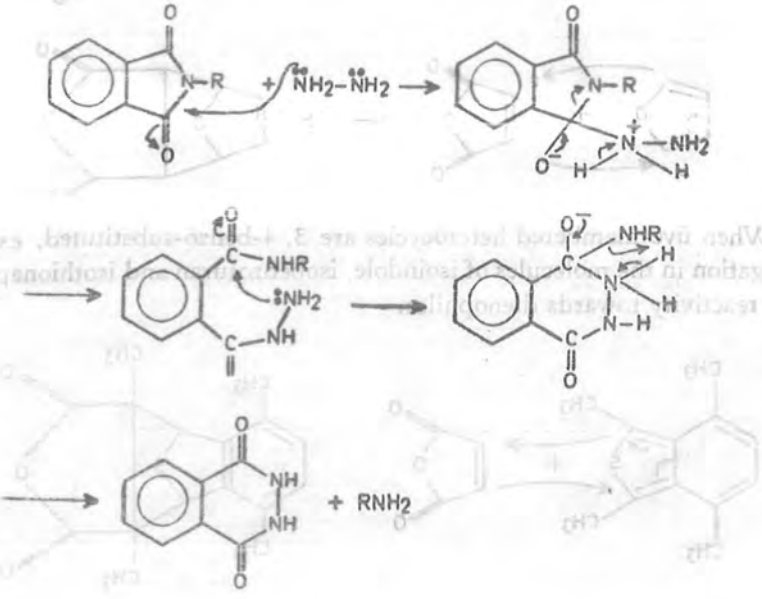


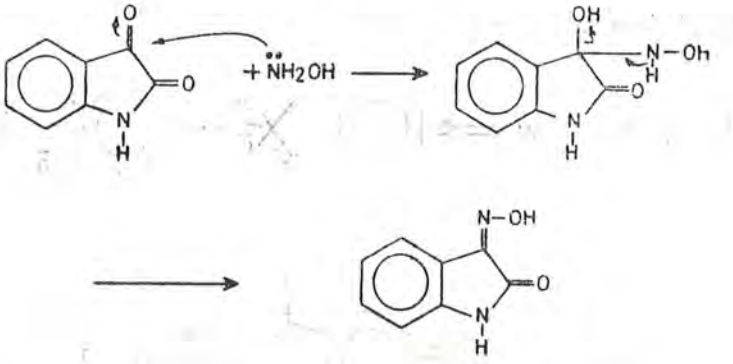
Pyrroles, furans and thiophene when α-substituted by alkyl halide group, hydroxy methyl group or amino methyl group, the nucleophilic displacement of the halide, hydroxyl or amino function is facile involving intramolecular rearrangement. Therefore entering group is substituted at α-position in the heterocycle.



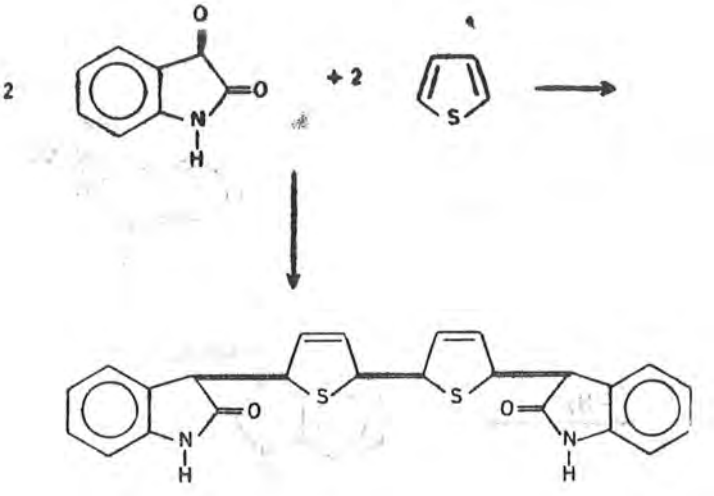
L = halide , $\bar{O}H$, $\bar{N}R_2$

Ring-open products are formed from five member heterocycles containing a carbonyl group adjecent to the hetere atom when treated with nucleophilic agents. The ease with which ring cleaves is dependent on the capicity of the hetero atom to localise the negative charge. Thus the order of reactivity is S > O > NH. However when both the α-position in the heterocyclic ring are blocked by carbonyl groups the ring fission is eased. The attack by a strong nucleophilic agent on the carbonyl function adjacent to the hetero-atom usually proceeds by ring opening. Phthalimide gives 1, 4-phthalazinedione on reaction with hydrazine.





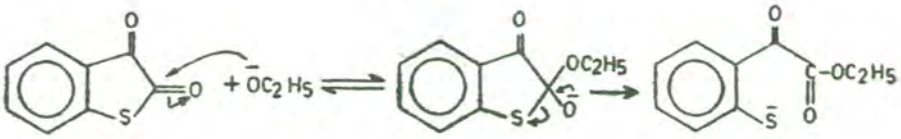
Similarly isatin give a color test with thiophene as a result of condensation between the methylene groups of thiopene molecule (in which both the positions are unsubstituted) and 3-carbonyl group of the isatin. It is known as indophenine test.



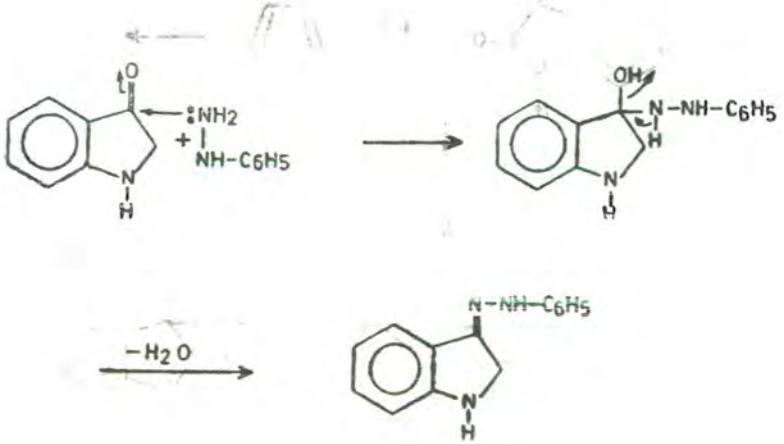
Indophenine

Similarly ions derived from oxindole and indoxyl show reaction with isatn to give isoindigo and indirubin each showing a nucleophilic attack by the methylene group at 3-and 2-carbonyl groups respectively.

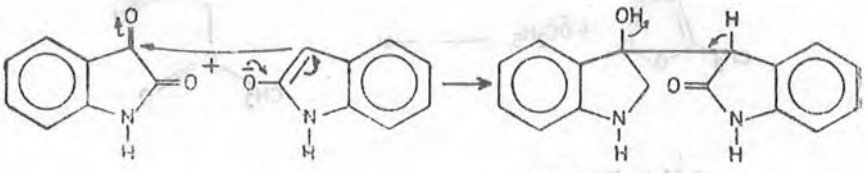
Similarly 2-coumaranone, its s-analogue and the diones react with hydroxide and alkoxide ions to give acid and esters.



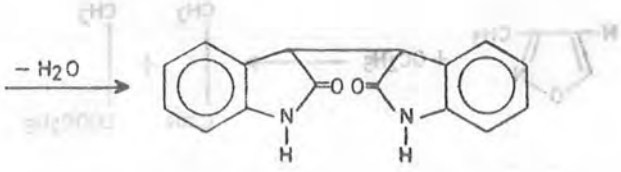
When carbonyl function is not adjacent to the hetero-atom in the ring then weak nucleophilic agents are required for ring substitution because carbonyl group is less stabilized by resonance as it is away from the hetero-atom. Therefore addition by the nucleophile is followed by spontaneous elimination of water. For instance indoxyl gives phenyl hydrazone when treated with phenyl hydrazine.



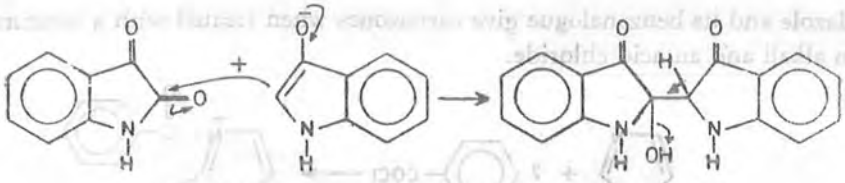
However, if both the carbonyl functions are present at 2-and 3-position then carbonyl at 3-position is preferentially attacked. Therefore isatin gives as oxime when treated with hydroxylamine. O-and S-analogues of the NH-compound are also reactive.

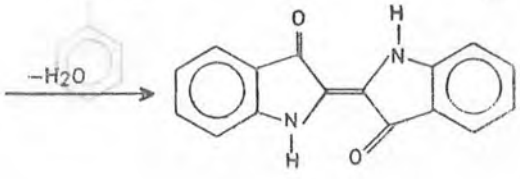


Isatin Oxindole



Isoindigo





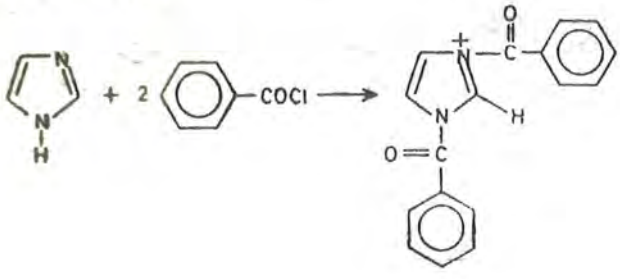
Indirubin

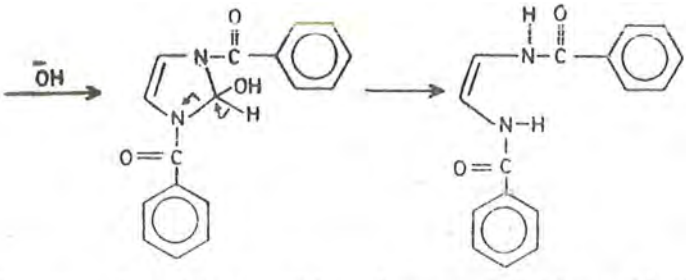
Nucleophilic attack at the ring carbons of five membered rings with two or more hetero atoms occurs readily because of the inductive electron withdrawing effect of the heteroatom and ring-opening products are formed. Iso-oxazoles when unsubstituted at 3-position give β-ketonitriles ; when substituted at 3-position but unsubstituted at 5-position give both acids and nitriles on reaction with ethoxide ions.

5-Methylisoxazole

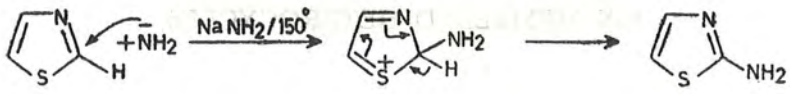
3-Methylisoxazole

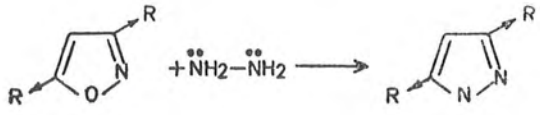
Imidazole and its benzanalogue give carbazones when treated with a mixture of an alkali and an acid chloride.





Thiazoles are aminated in 2-position when treated with amide ions, while isoxazoles give pyrazoles with hydrazine by some internal rearrangement reaction.

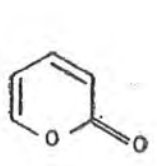

N
S
H
+NH2
Na NH2 / 150°
N
NH2
S
H
N
S
NH2


R
N
O
R
+NH2–NH2
R
N
N
R

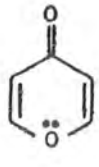
SIX MEMBERED HETEROCYCLES

Pyrans and Related Compounds

Carbonyl derivatives of pyrans are known as α-pyrone and γ-pyrone and are feably aromatic.

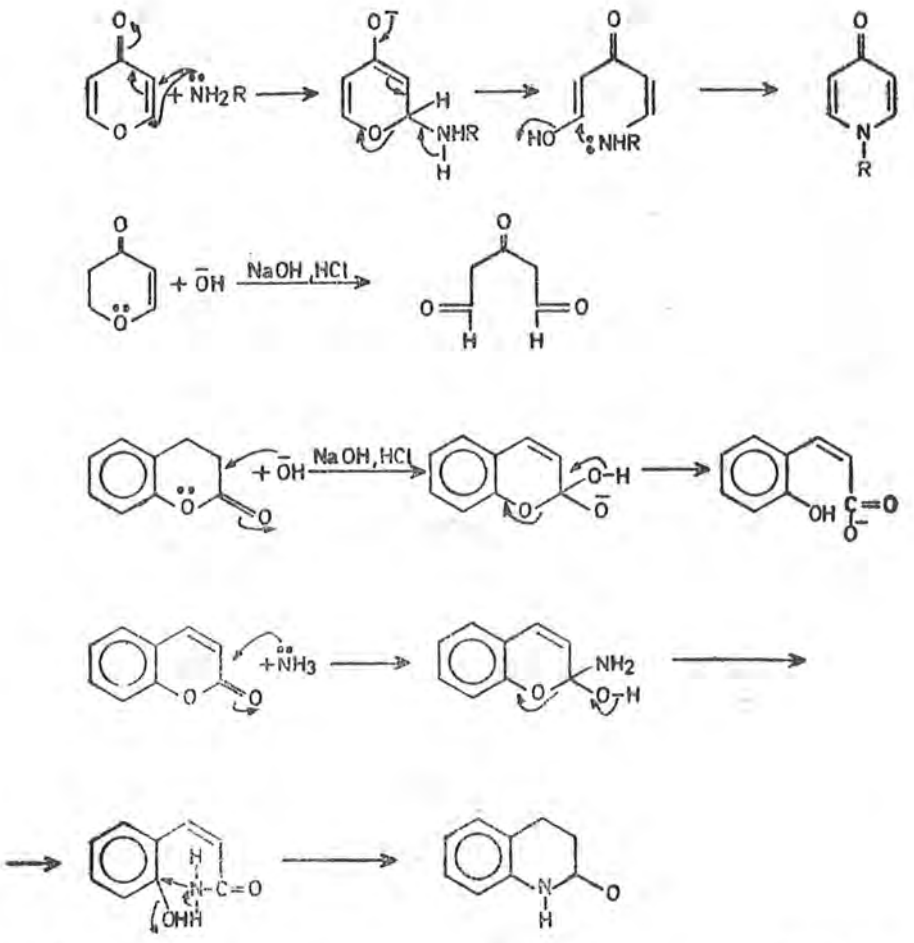


α -PYRONE

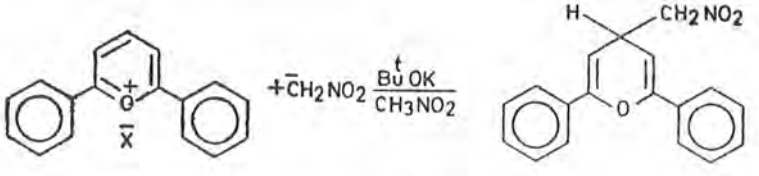


γ-PYRONE

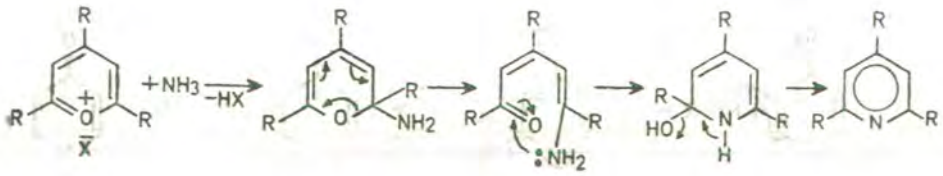
However, α-pyrone is less reactive than its other isomer due to lesser aromatic character. γ-pyrone is attacked by the nucleophiles at α-carbon atom only and ring opened product are usually formed, while in the case of α-pyrone carbonyl function is attacked due to its viscinity to the oxygen atom of the ring making the carbonyl carbon electrophilic towards attack by a nucleoplhile.



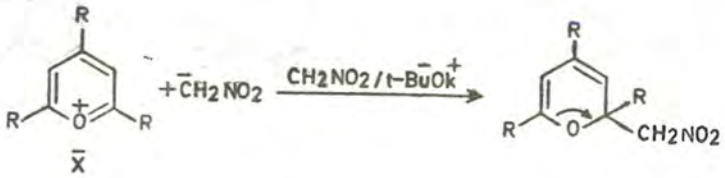
Pyrylium salts give γ-substituted products when α-positions are blocked in the ring when treated with carbanions.

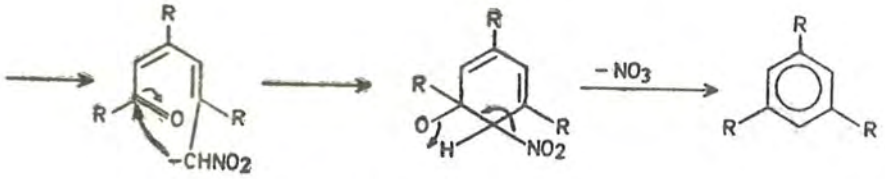


However when α-and γ-position are substituted by alkyl groups the addition of the nucleophile is mainly at α-position due to the neighbouring electronegative oxygen atom. This effect is diminished largely at γ-position. Therefore products are formed by ring-opening and subsequent ring-closure transformations.

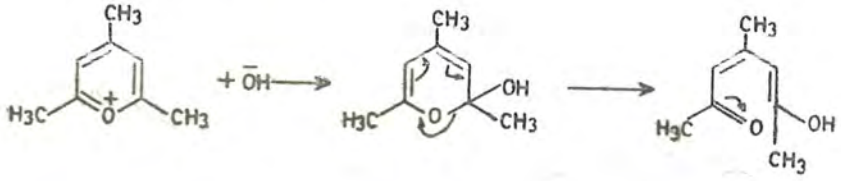


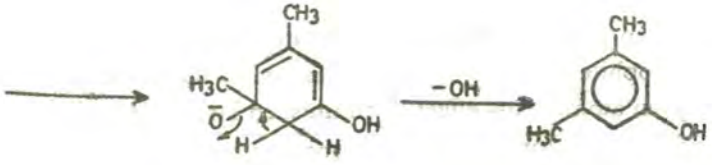
Nucleophiles like $\overline{CN}$, $\overline{H}$, $\overline{Ph}$ and amines result identical reactions and the open-chain stable dienones are formed prior to ring closure in these reactions through the nucleophilic added. However, when ring-closure occurs through ring substituent then carbocyclic rings are formed. These reactions are carried out in a strong basic medium and the resulting dienone formed in the ring-opening step is either derived by the addition of a carbanion or in the resulting dienone by nucleophilic addend.



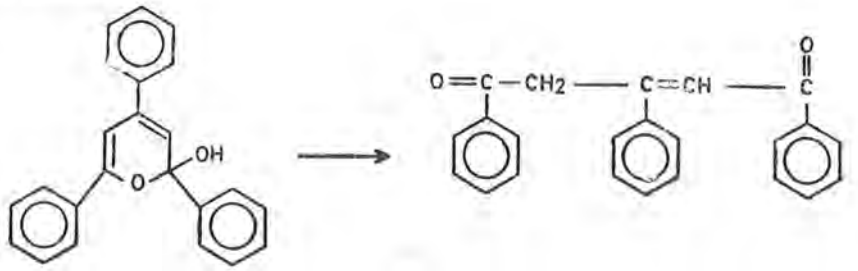


R = alkyl, phenyl

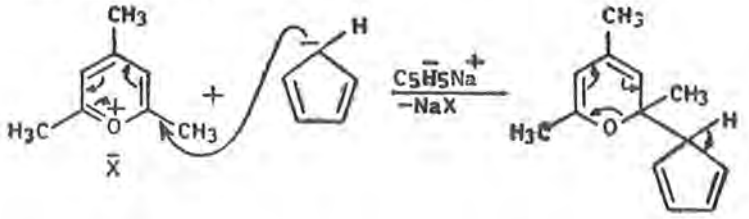


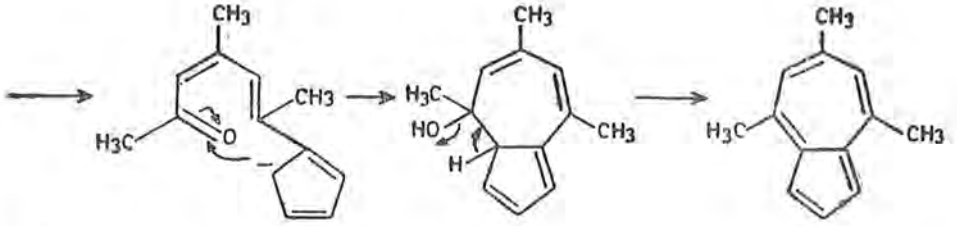


However when the pseudo-base is substituted by an electron withdrawing mesomeric group then only open chain diketones are produced by rearrangement processes.



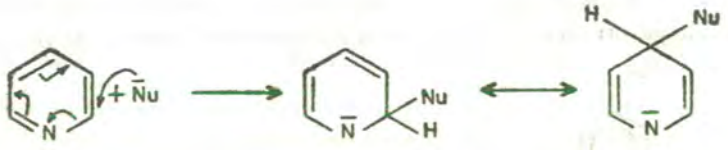
Cyclopentadienide anion results in ring enlargement product (azulenes) when treated with pyrylium salt.





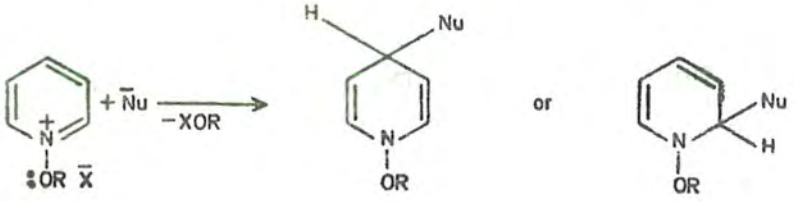
Pyridine

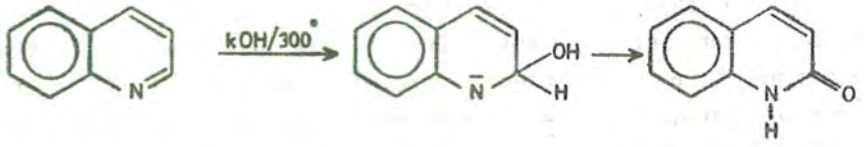
Aromatic nucleophilic substitution on the pyridine ring is facile due to the accomodation of the negative charge on the hetero atom and is a characteristic of the pyridine ring as compared to benzene. This happens because nitrogen atom is more electronegative than the ring carbons and therefore it helps electron disolacement towards itself in the ring allowing the nucleophilic attack at the α-position or γ-position which are resonance stabilised.



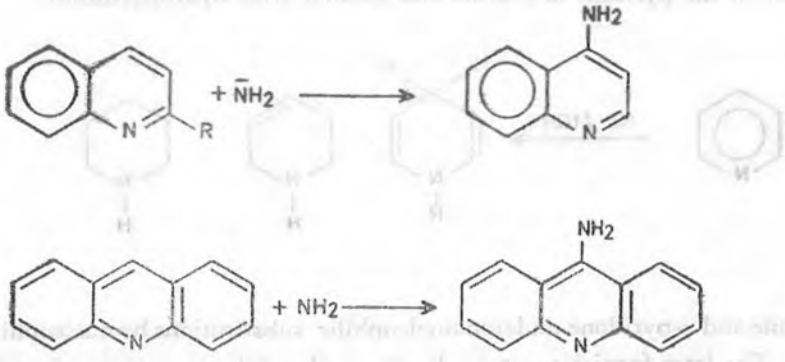
The initial formation of the adduct thus undergoes rearomatisation by the loss of the hydride ion to give an addition product.

Electron-withdrawing substituents on nitrogen and fused benzene systems attached to pyridine ring facilitate the attack by the nucleophile.

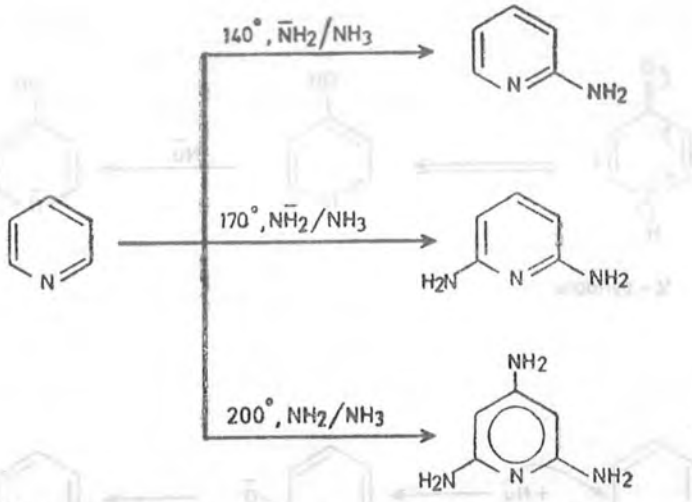




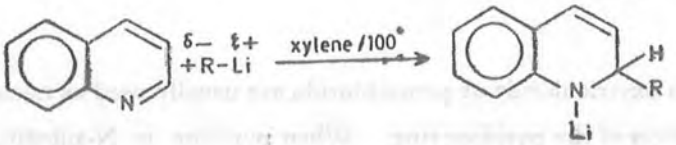
When α-positions in pyridine ring are blocked then attack by the nucleophile occurs at γ-position.



The reaction of pyridine with amines is very slow and a stronger basic nuclephile is usually used. The substitution of the ring is temperature dependent.

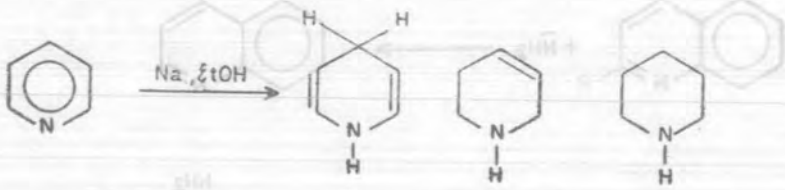


Organometallics react under vigorous conditions and give α-substituted pyridine. Benzopyridines give similar reaction unless α-positions are blocked by ring substituents. Dihydro-derivatives of the benzopyridines are stable and can be isolated.

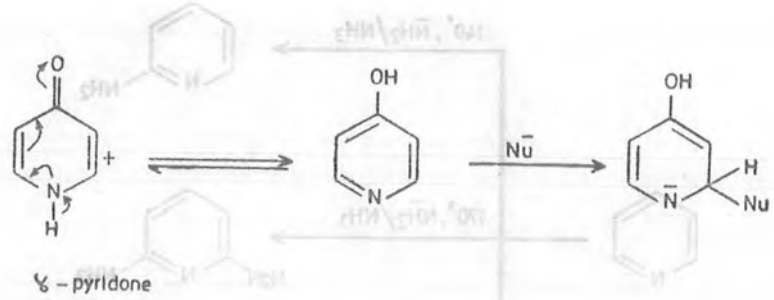


R = alkyl or aryl

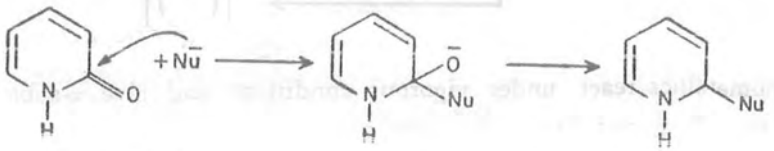
Reduction of the pyridine in sodium and ethanol gives hydropyridines.



α-Pyridone and γ-pyridone undergo nucleophilic substitutions by nucleophilic agents. The later furnishing attack by the nucleophile at α-position while in the former carbonyl carbon, attacked by the loss of carbonyl oxygen followed by rearomatisation.

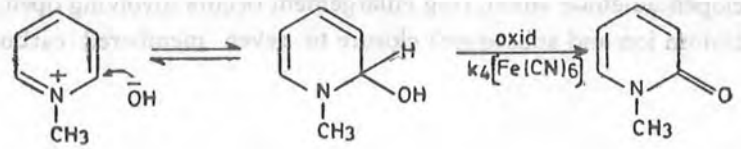


γ - pyridone

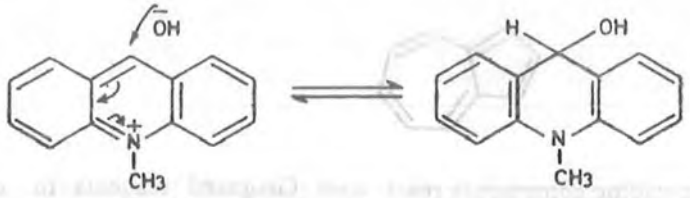


α - pyridone

Phosphorous oxytrichloride or pentachloride are usually used as nucleophiles for chlorination of the pyridine ring. When pyridine is N-substituted by an alkyl group it forms a pseudo-base at the α-position on treatment with alkali. However benzopyridines form these bases readily (aromaticity is lost only in the pyridine ring) and are stable compounds.

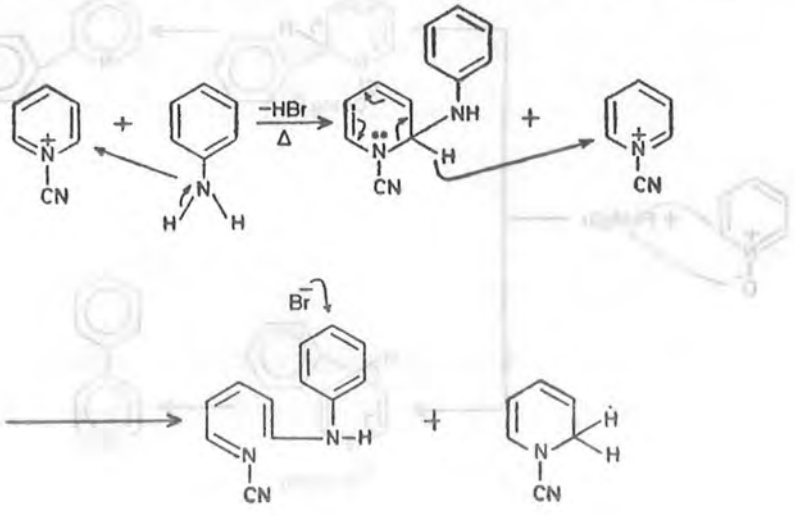


In case of acridinium the pseudo-base adduct is formed only by substitution at γ-position.

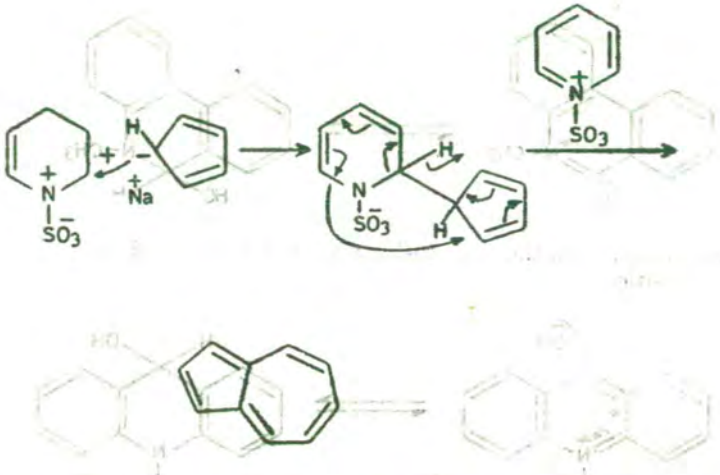


and aromaticity of the benzene ring alongwith the pyridine ring is distorted. However these bases are oxidised to pyridones on treatment with potassium ferricyanide.

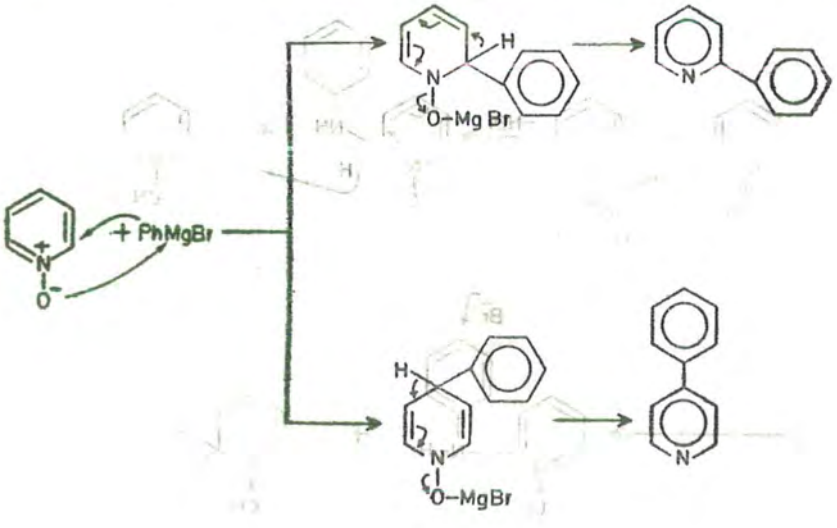
When pyridine is N-substituted by electron-withdrawing groups, it undergoes ring fission on treatment with alkali under mild conditions.

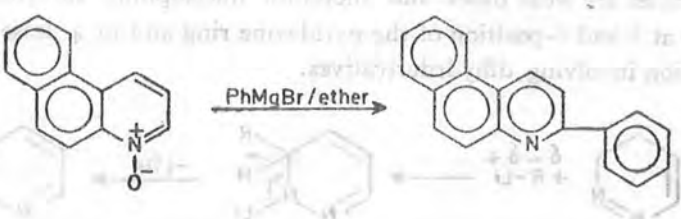


With cyclopentadienide anion. ring enlargement occurs involving opening of the pyridinium ion and subsequent closure to seven membered carbocyclic ring.

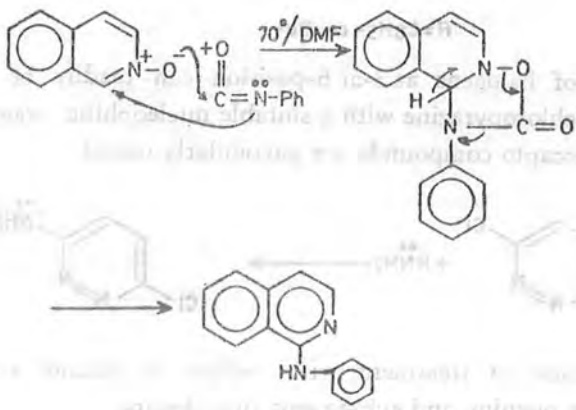


N-oxides in pyridine compounds react with Grignard reagents in ether. In these reactions deoxygenation of the N-oxide group is accompanied by substitution at α-or γ-position with respect to the nitrogen atom of the ring.

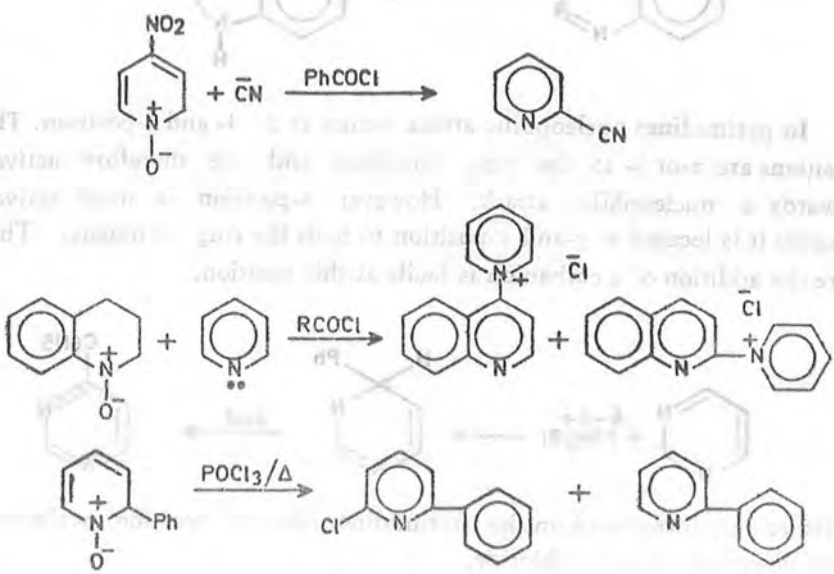




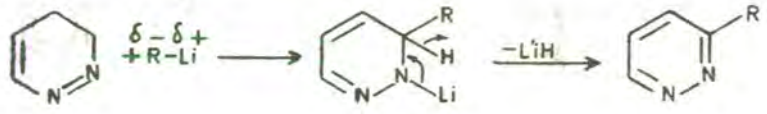
Carbimides add nucleophilically to these systems involving 1,3-dipolar cycloaddition reactions.



While nucleophiles like $\overline{CN}$, amines and halide ions give ring subttituted products.



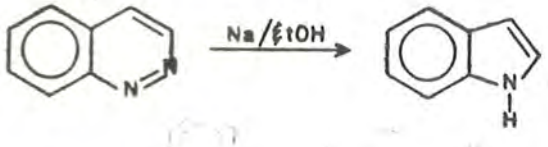
Pyridazines are weak bases and therefore nucleophilic substitution occurs readily at 3-and 6-position of the pyridazine ring and to a lesser extent at 4-position involving dihydrderivatives.



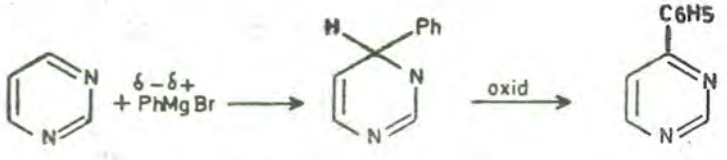
R=C_6H_5- or Bu-

Displacement of halogens at 3-or 6-position can readily be achieved by treating 3,6-dichloropyrazine with a suitable nucleophilic reagent. Alkoxy, amino and mercapto compounds are particularly useful.

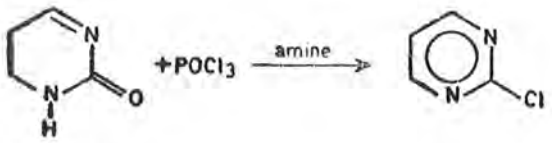
Benzopyridazines on treatment with sodium in ethanol are reduced to indoles by ring opening and subsequent ring closure.



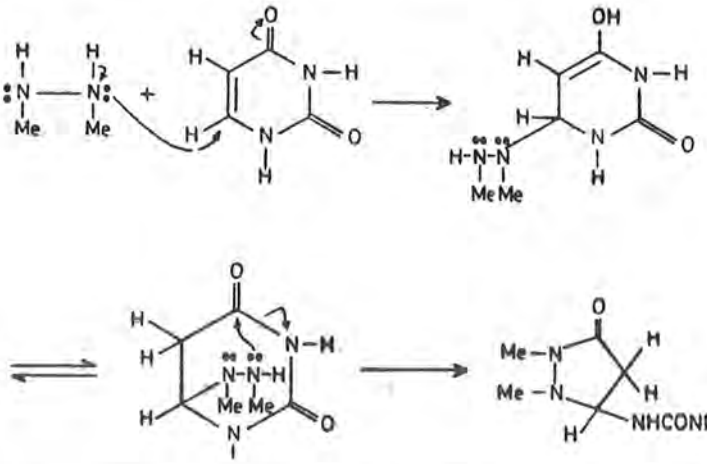
In pyrimidines nucleophilic attack occurs at 2-' 4- and 6-position. These positions are α-or β- to the ring nitrogens and are therefore activated towards a nucleophilic attack. However 4-position is most activated because it is located at γ-and α-position to both the ring nitrogens. Therefore the addition of a carbanion is facile at this position.



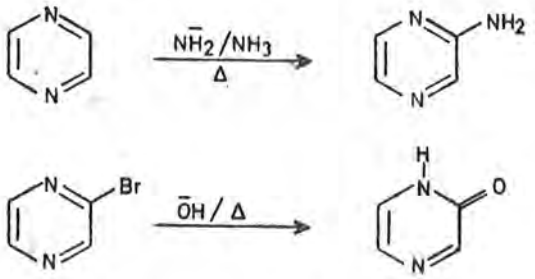
Halogens are introduced on the pyrimidine ring by treating pyrimidones with phsophorous oxytrichloride.



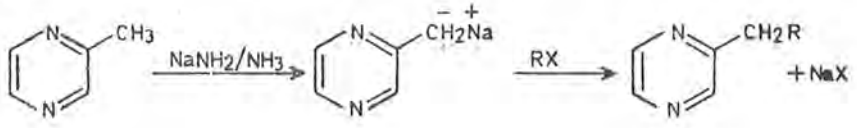
Hydrazine and its derivative reduce the pyrimdine to pyrazolone by the enclosure of the ring and recyclisation.



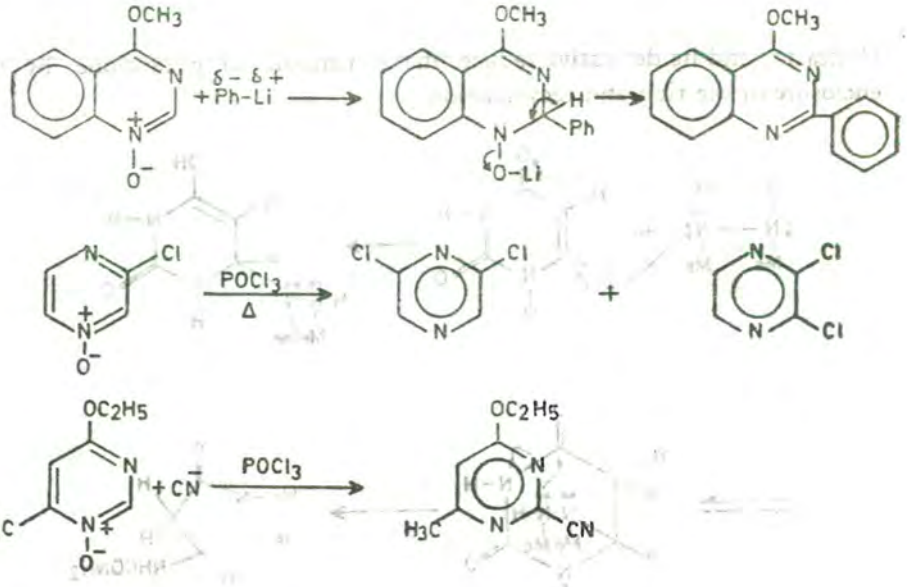
Pyrazines with amide ion are aminated at a position which is ortho to the ring nitrogen. It also reacts with alkali to give pyrazinone.



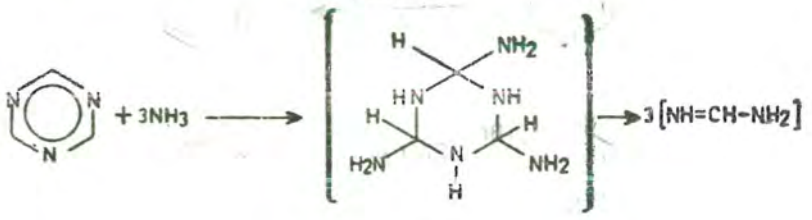
When ring substituent is an alkyl group at α-or γ-position, it gives a carbonion first and then side chain can be increased by the use of proper reagents.

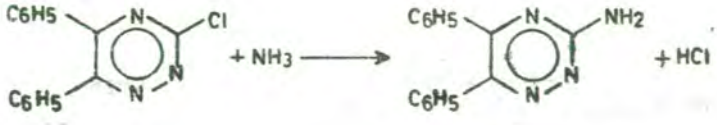


Other N-oxides of the nitrogen heterocyclic ring system containing more than one nitrogen give expected nucleopilic substitution at α-or γ-position. Some examples are quoted below.

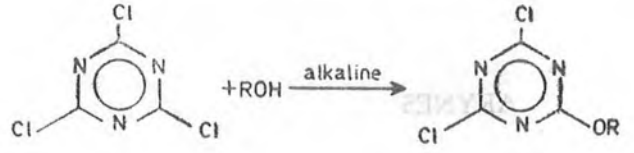


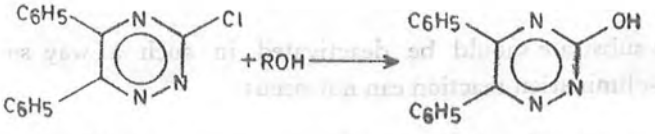
S-Triazine and 1, 2, 4-triazine undergo ring nucleophilic substitution when treated with amines. The former gives amidines by ring opening while later is substituted at α-position or γ-position born by the same carbon at a time with respect to the ring nitrogens by displacement of chloride ion.



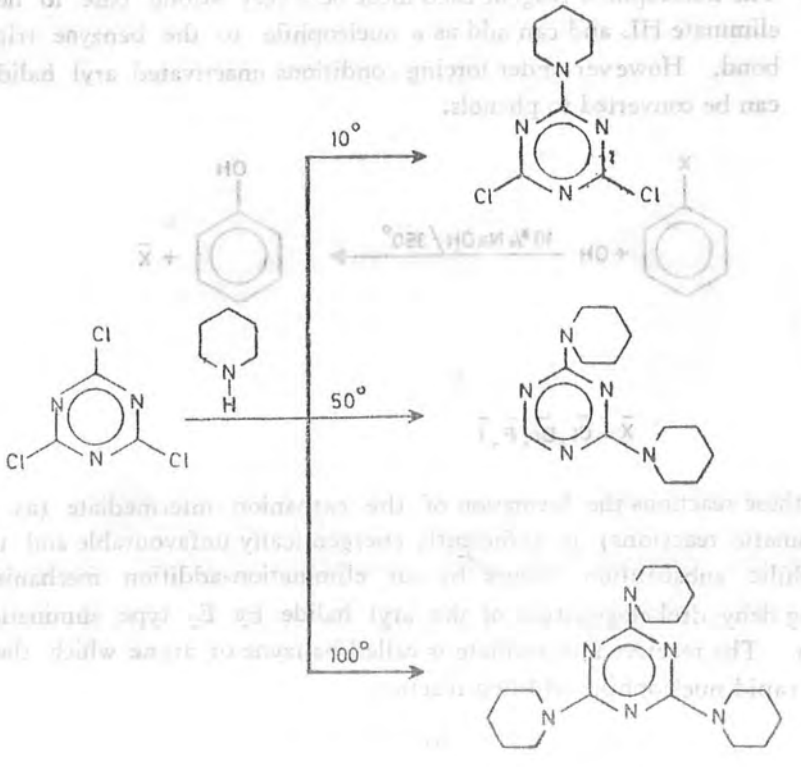


On treatement with alcohol both triazines give α-substituted product.





While dehalogenation of s-triazine is temperature dependent with synchronous addition of the amine nucleophile.



ARYNES

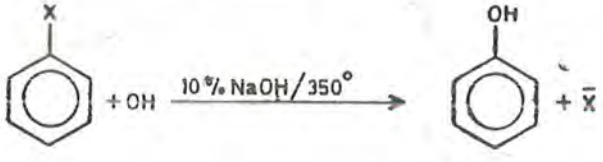
Benzynes

For an elimination-addition reaction three factors are considered generally.

(a) The aromatic substrate should be deactivated in such a way so that addition-elimination reaction can not occur.

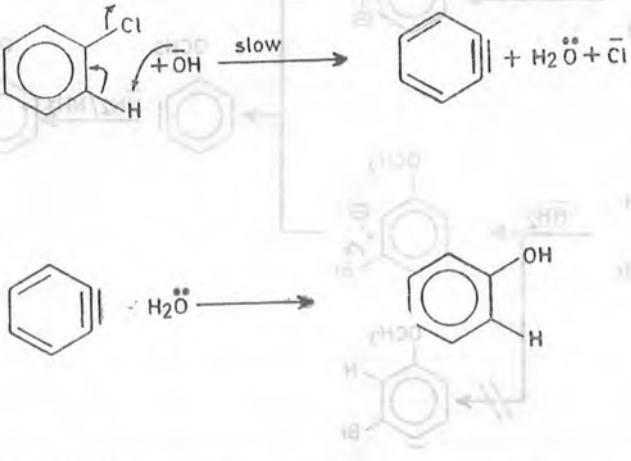
(b) The presence of ortho hydrogen to a group L (sufficiently electronegative and good leaving) be rendered acidic to be removed as a proton and group L with its bonding electron pair to eliminate HL from the aromatic substrate resulting a benzyne, Group L may be a halide.

(c) The nucleophilic reagent used must be a very strong base to help eliminate HL and can add as a nueleophile to the benzyne triple bond. However under forcing conditions unactivated aryl halides can be converted to phenols.

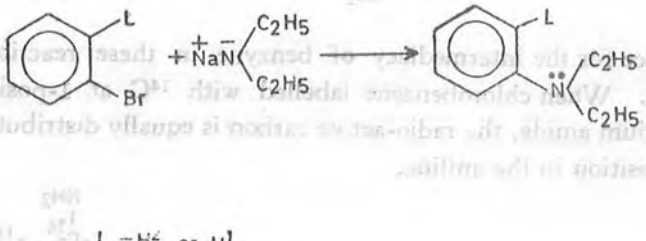


$\bar{X} = \bar{Cl}, \bar{Br}, \bar{F}, \bar{I}$

In these reactions the formation of the carbanion intermediate (as in SN_2 aromatic reactions) is sufficiently energentically unfavourable and the nucleophilic substitution occurs by an climination-addition mechanism involving dehy drohalogenation of the aryl halide by E_2 type elimination reaction. The reactive intermediate is called banzyne or aryne which them follows rapid nucleophilic addition reaction.

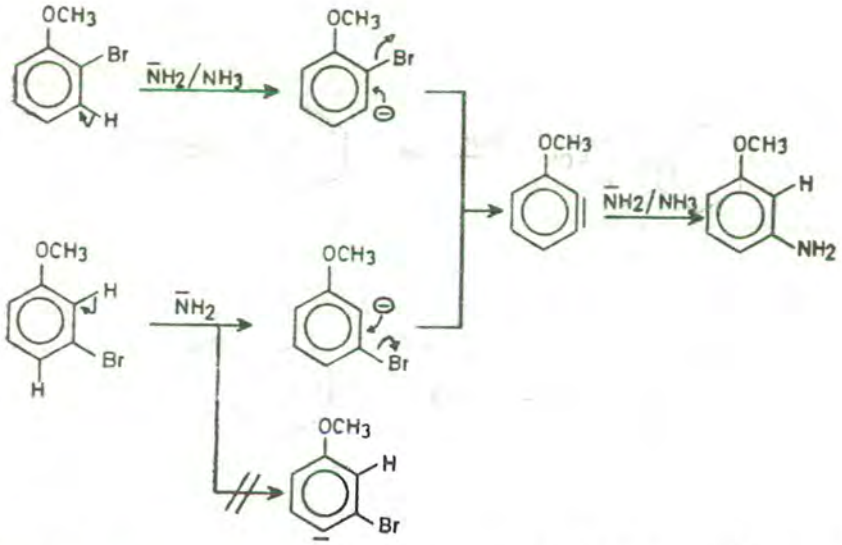


In the formation of the benzyne only aryl hydrogens are removed by strong bases. This is observed by the comparison of bromobenzene-2-D which reveals a large deuterium isotope effect of 5.7 in diethylamide ions.

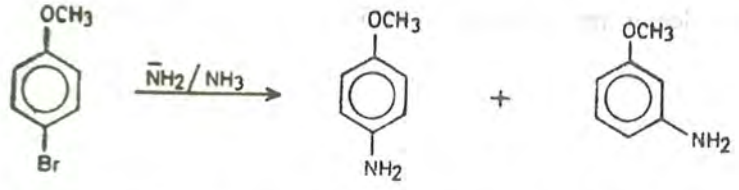


L = H or H

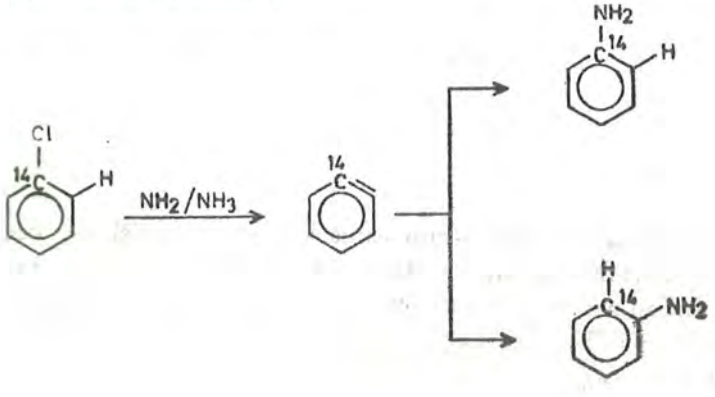
Both m-bromoanisole and o-bromoanisole yield m-anisidine because they form the same benzyne intermediate. The negative charge of the anion is on the carbon next to the electron-withdrawing group. Addition of amide ion occurs in such a way that the negative charge appears on the carbon next to methoxyl group.



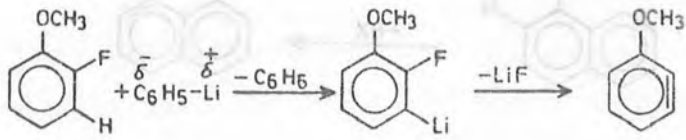
When p bromoanisole is treated with potassium amide in liquid ammonia, a mixture of meta and para anisidines is obtained.



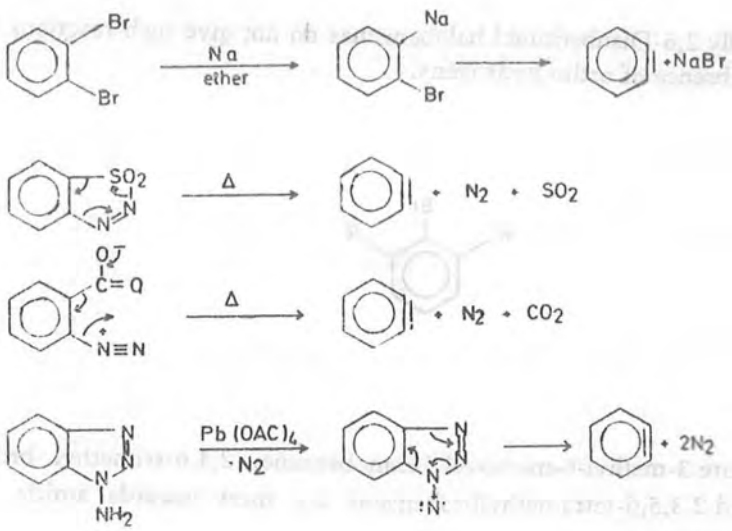
The evidence for the intermediacy of benzyne in these reactions is well established. When chlorobenzene labelled with ^{14}C at 1-position reacts with potassium amide, the radio-active carbon is equally distributed between 1- and 2-position in the aniline.



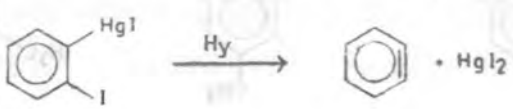
Generation of benzynes also involves the use of organolithium compounds. In the reaction of phenyllithium with flouroanisole a proton is abstracted by the phenyl anion which loses fluoride ion to give a benzyne.



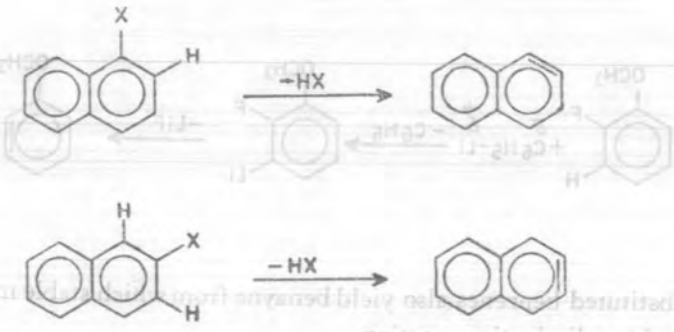
Ortho-Disubstituted benzenes also yield benzyne from which stable molecules can be formed by elimination reaction.



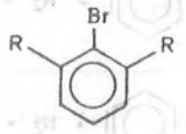
Photolysis of O-disubstituted benzenes also afford benzyne.



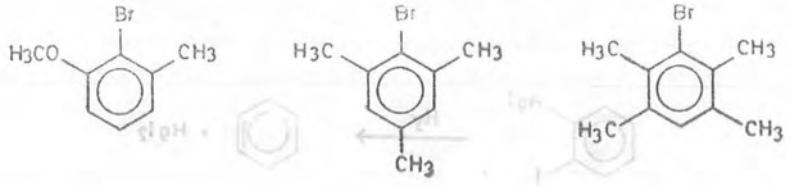
Halonaphthalenes substituted at 1- or 2-position yield corresponding aryne when treated with piperidine.



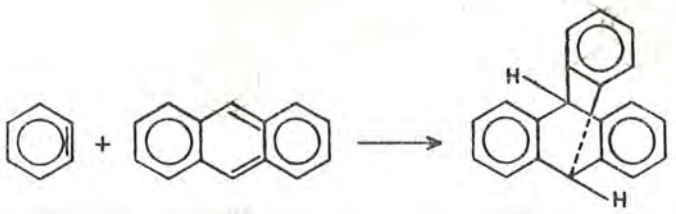
Generally 2,6-Disubstituted halobenzenes do not give such reactions because of the absence of ortho hydrogens.

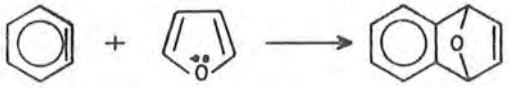


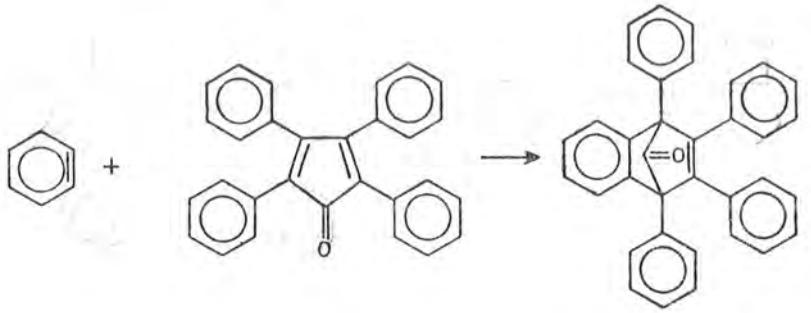
Therefore 3-methyl-6-methoxyl bromobenzene, 2,4,6-trimethyl bromobenzene and 2,3;5,6-tetramethylbrobenzene are inert towards amide ions in liquid ammonia.

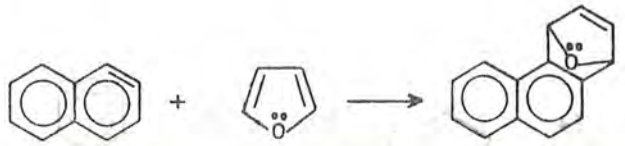


The benzynes serve as dienophile in the presence of dienes in the reaction mixture and addition products are obtained.



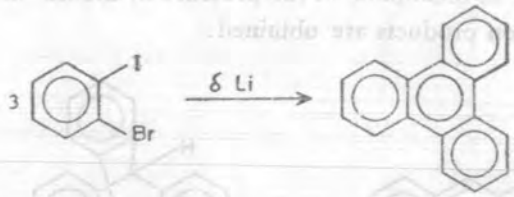




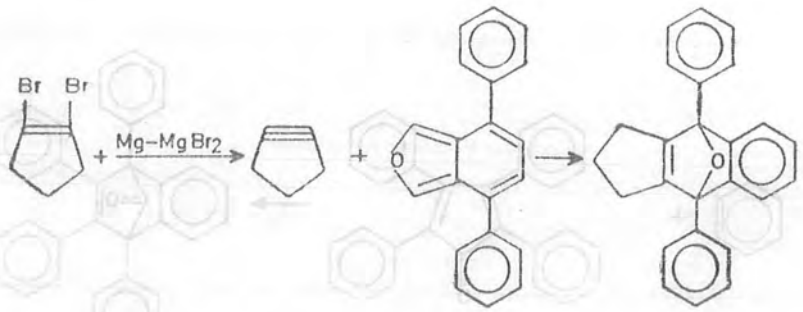


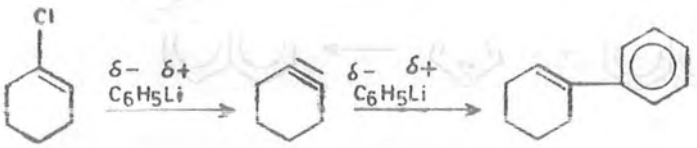
In the absence of dienes benzyne dimerizes to biphenylene.

Triphenylene, a trimer of benzyne is formed when dihalobenzene reacts with metallic lithium.

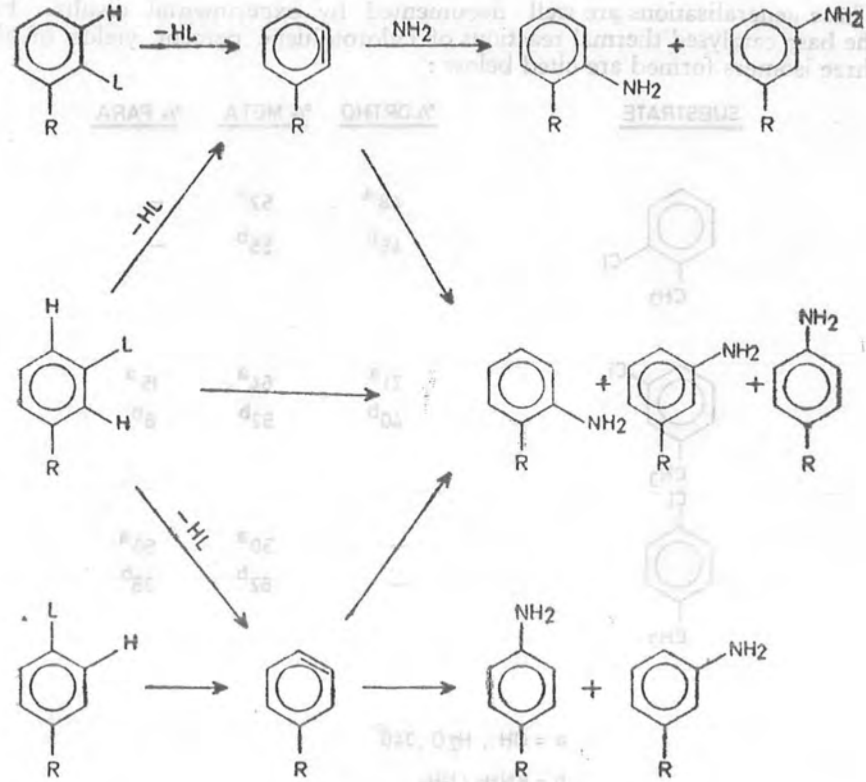


Aryne intermediates are not restricted to aromatic systems. Cyclopentyne and cyclohexyne are produced by treating dibromocyclopentene and 1-chlorocyclohexene with Mg and phenyllithium respectively.



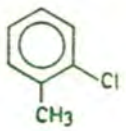
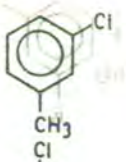
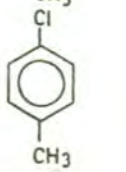


Ortho disuhstituted and para disubstituted benzenes form a single benzyne intermediate with alkali metal amides in ammonia while meta disubstituted benzenes form two different benzynes. The following products are expected in which ortho meta and para reactants yield ortho and meta; ortho, meta and para; meta and para products respectively.



R = Activating substituent , L = Good leaving group

These generalisations are well documented by experimental results. For the base catalysed thermal reactions of chlorotoluene percent yields of the three isomers formed are cited below :

SUBSTRATE	% ORTHO	% META	% PARA
	48[a] 45[b]	52[a] 55[b]	– –
	21[a] 40[b]	64[a] 52[b]	15[a] 8[b]
	– –	50[a] 62[b]	50[a] 38[b]

a = OH , H_2O , 340°

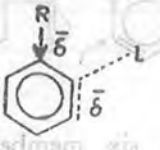
b = KNH_2/NH_3

The orientation of the benzyne formed depends-upon the acidity of the hydrogens to be eliminated. This is controlled by the inductive effect of the ring substituent and falls true for the subsequent nucleophilic addition. The nucleophile attacks the benzyne sp_2^- bond which is coplanar with the ring and at right angles to the aromatic π-system thus making the conjugative transmittance due to the ring substituent ineffective as can be seen from the rate constants for benzyne formation at 20° from arylbromide and lithium piperidide in pyridine.

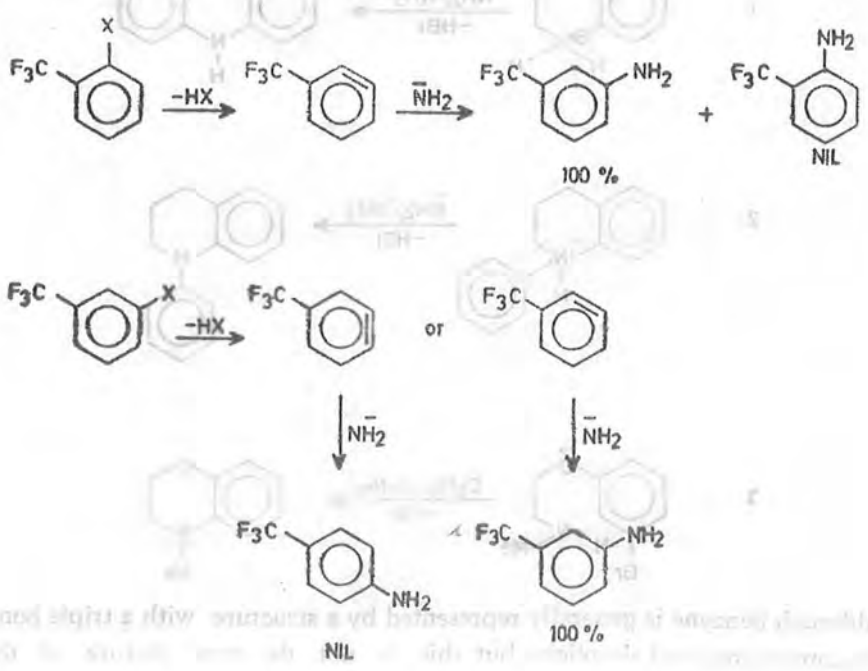
SUBSTITUENT	$10 \times k_2$ L mole^{-1} . sec^{-1}
–H	11.7
O–CH_3	2.9
m–CH_3	4.25
p–CH_3	5.3
p–C_6H_5	29.7
O–OCH_3	8.2
m–OCH_3	33.00
p–OCH_3	13.8

The incoming nucleophile (in the addition stages) attacks at the region of least electron density and therefore electronwithdrawing (activating) substituents favour the reaction at a more distant position because electrons of the sp^2-π bond of the benzyne are closer to the electron-deficient carbon linked with the substituent.

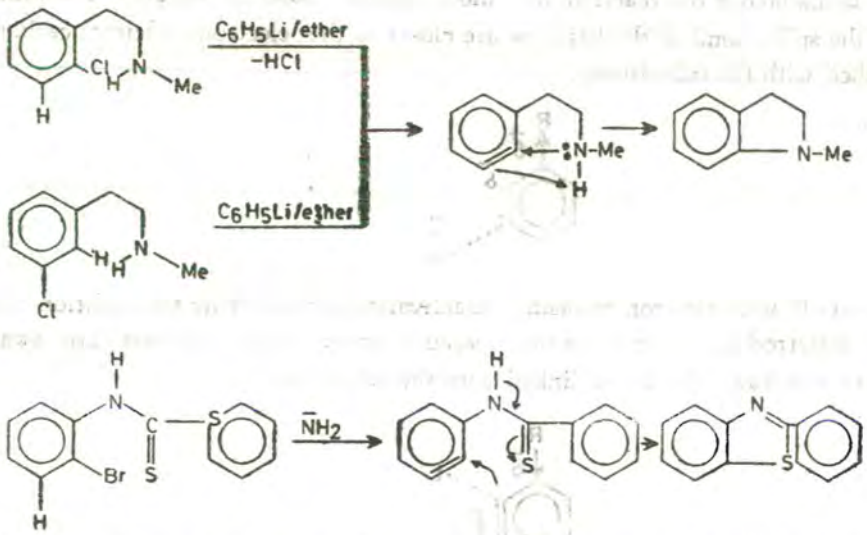
Similarly with electron releasing (deactivating) substituents the addition will be preferred to a nearer position because sp^2-π bond electrons are away from electron-rich carbon linked with the substituent.



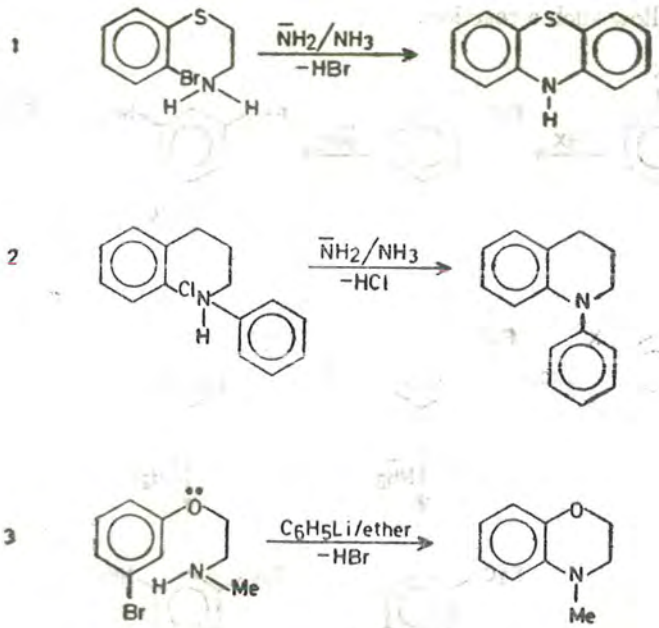
For instance electron-withdrawing substituent (CF_3 group) on a halogenobenzene follow such a reaction.



The presence of benzyne is confirmed in organic syntheses which involve such intermediates from ortho disubstituted and meta disubstituted benzene compounds.



Other similar reactions in which six membered rings result are as follows :—



Although benzyne is generally represented by a structure with a triple bond for convenience and simplicity but this is not the true picture of the

intermediate. Triple bonded carbons are sp-hybridised, linear and posess bond angle equal to 180°. A linear arrangement of two sp-hybridised carbons can not be shown in a cyclic six-membered system. The actual structure is unknown. It has been suggested that the intermediate has all the carbon sp^2-hybridised but the third bond which is a new sp^2-π-bond is in the plane of the ring and involves overlap of the sp^2-hybrid orbitals due to two sp^2 electrons on the neighbouring carbon with anti-parallel spins. Thus the new bond (sp^2-π bond) is different and weaker than p-π bond.

p_π orbitals in benzene

The strain caused by sp^2-π bond orbital is decreased when ring becomes larger thus cycloctyne is in fact isolable and a somewhat stable compound.

Hetaryne

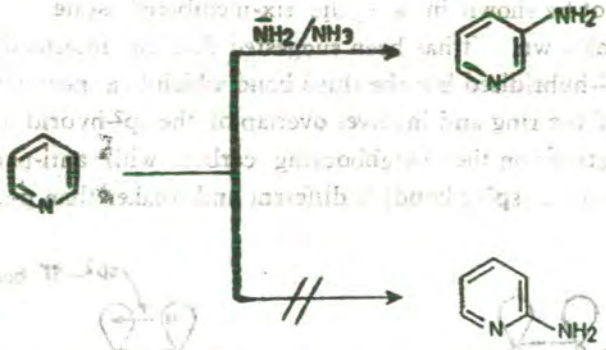
Hetaryne is heterocyclic analogue of benzyne. The species known in pyridine system are represented as follows :-

2,3-pyridine

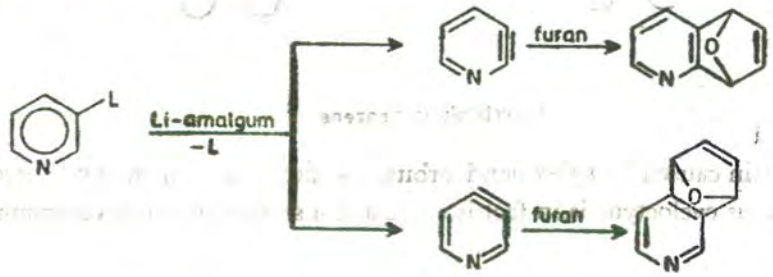
3,4-pyridine

The additional π-bond is formed due to the paired electrons, the p-orbital is coplanar with the pyridine ring and can be represented in a similar way as benzyne. Both the species are possible from 3-chloropyridine but 3,4-pyridyne is easily formed and is more stable than 2,5-pyridyne becuase in the later species carbon-2 is next to the electronegative nitrogen and therefore explusion of carbon-3 substituted chlorine is difficult in elimination addition process due to lower mobility of hydrogen attached to corbons.

Therefore the absence of 2-substttuted pyridine suggests that 3,4-pyridyne is formed.



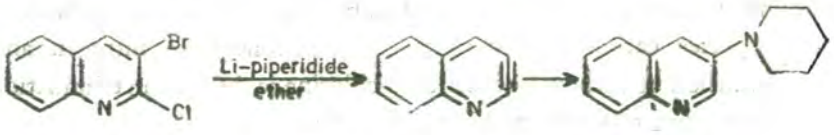
However, the presence of 2,3-pyridyne has been demonstrated when 3-bromo-2-chloropyridine is treated with lithium-amalgum in furan, when the species gives adducts.

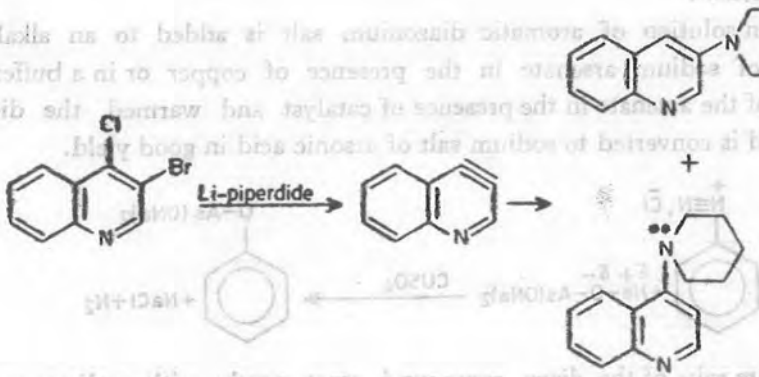


L = Cl , Br

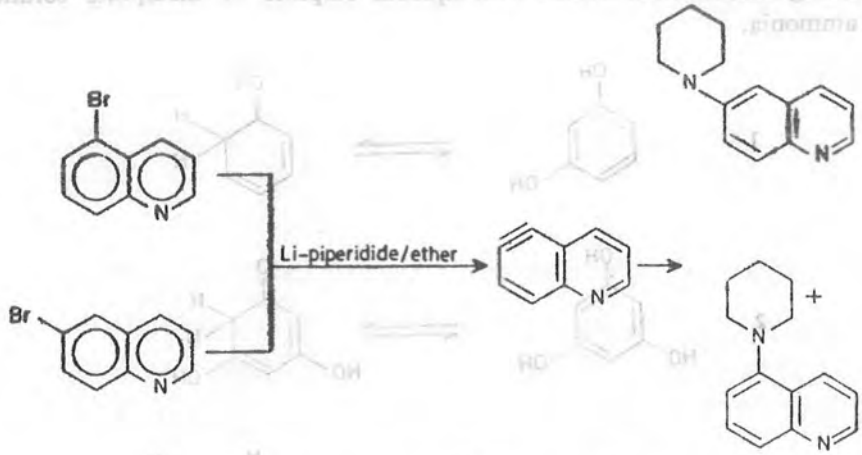
Reduction of both the adducts results quinoline and isoquinoline respectively. For the preparation of hetarynes essentially similar conditions are required as those for benzynes i.e. the use of strong bases, low reactivity of the substrate, presence of a good leaving group which should be sufficiently electronegative and the presence of ring hydrogens on neighbouring carbon to the carbon bearing the leaving group etc.

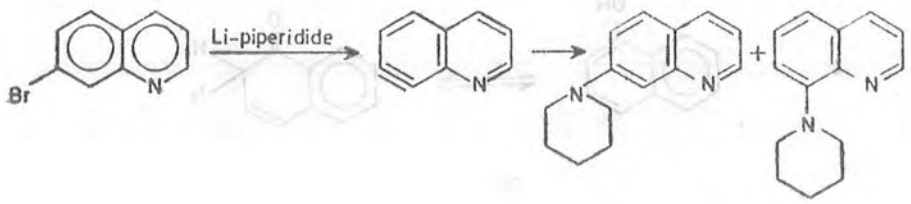
Quinolynes are produced from 3-bromo-2-chloroquinoline and 3-bromo-4-chloroquinoline with lithium-piperidide by nucleophilic addition reactions.





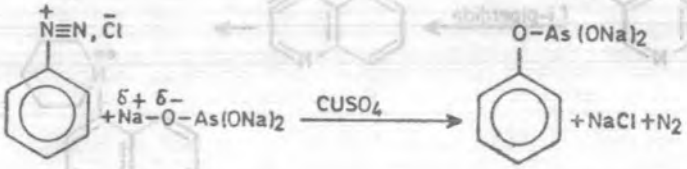
The presence of 5,6-quinolyne and 7,8-quinolyne has been demonstrated when the benzene ring is substituted by a halogen at 5- or 6-position and at 7-position respectively but when pyridine ring is unsubstituted.





Bart Reaction :

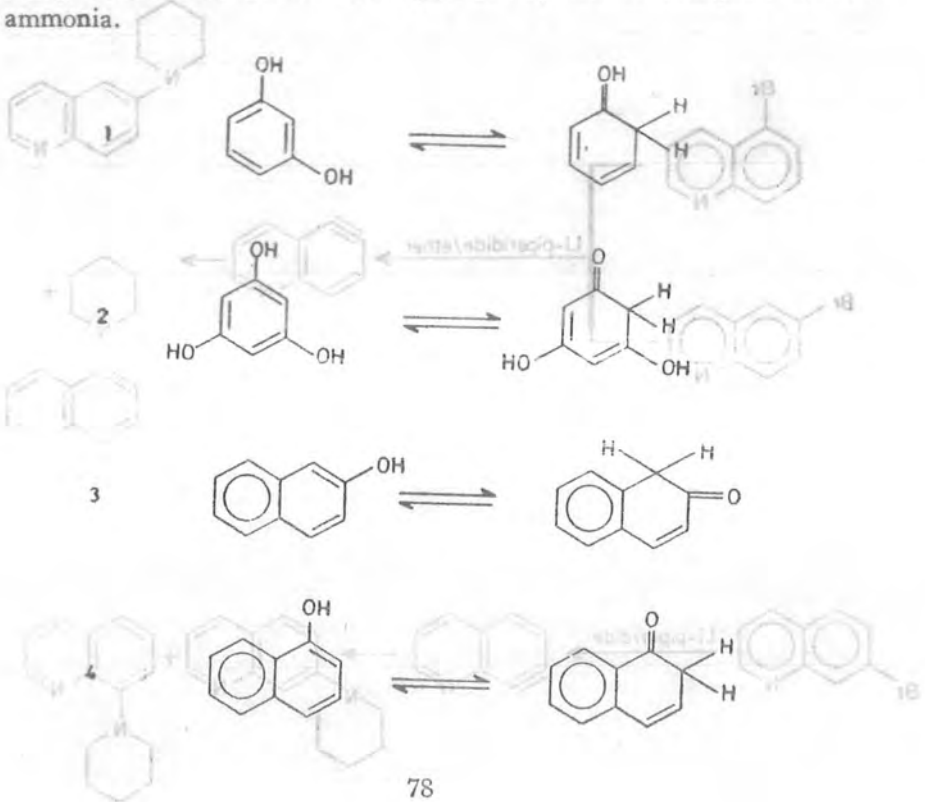
When solution of aromatic diazonium salt is added to an alkaline mixture of sodium arsenate in the presence of copper or in a buffered solution of the arsenate in the presence of catalyst and warmed, the diazo compound is converted to sodium salt of arsonic acid in good yield.



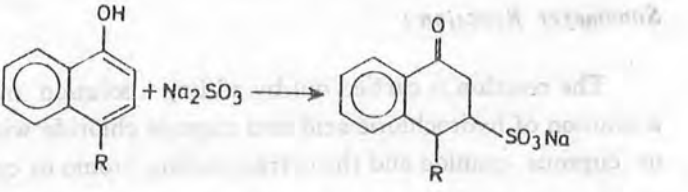
Fluorborate salts of the diazo compound react neatly with sodium meta arsenite in alkaline medium containing copper catalyst giving improved yield of the arsonic acid.

Bucherer Reaction :

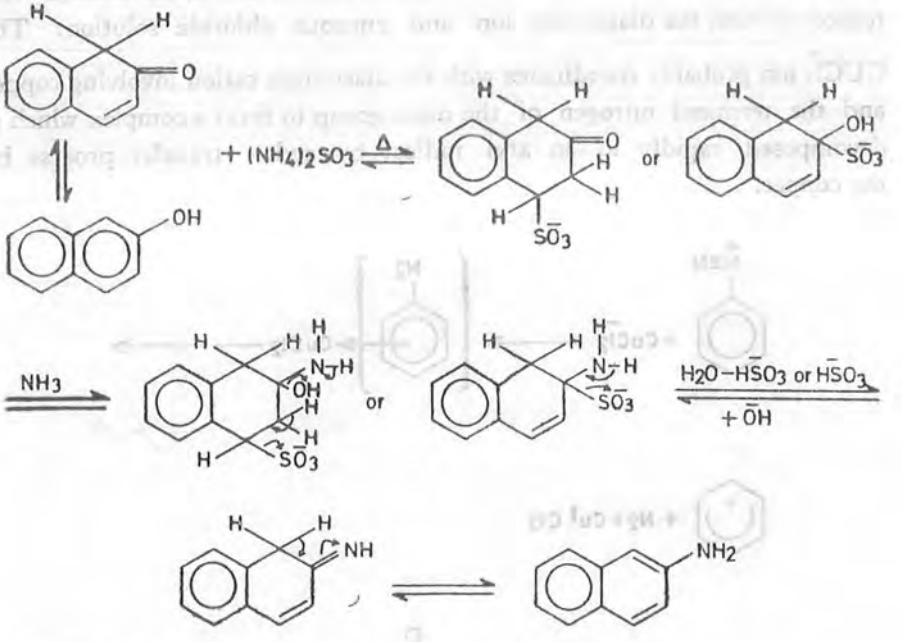
Phenols and naphthols which have tendency to ketomerise give corresponding amines when treated with aqueous sulphite or bisulphite solution in ammonia.



The reaction is believed to involve a bisulphite adduct of the keto-tautomer of the phenol. The formation of the adduct is the rate-determining step of the reaction. The addition product of an α-naphthol gives an addition product tetrahydro-4-oxo-2-naphthalenesulphonic acid.

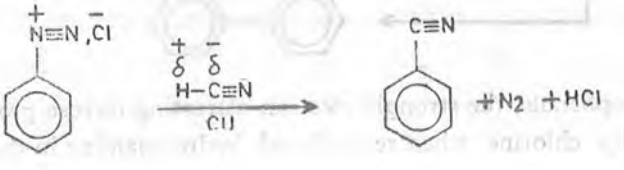


The reaction is a reversible one and therefore it is performed by heating with aquous ammonia and ammonium sulphite. For β-naphthol the reaction mechanism is as follows :—



Gatterman Reaction :

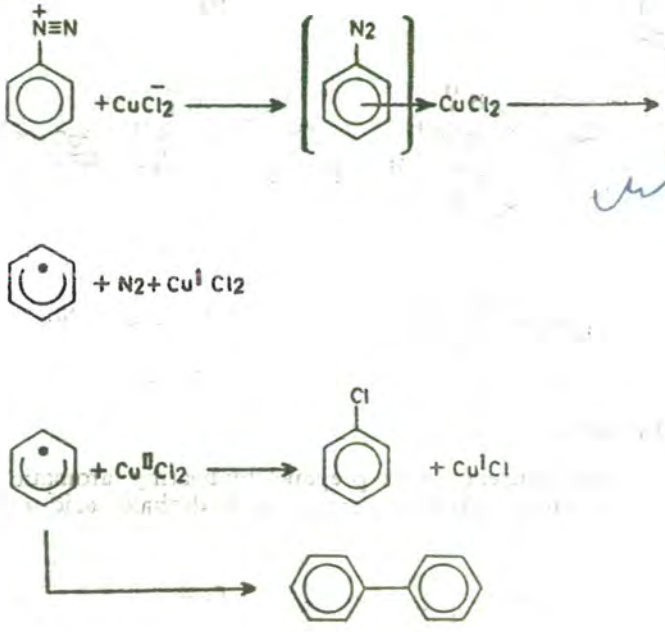
Halo-or cyanobenzene can be prepared by heating aromatic diazonium halide salt with finally divided copper in hydrohalo acid or hydrogen cyanide.



The reaction is not very commonly employed in organic synthesis because of low yield of the product and practical problems faced in purification of the product. The reaction proceeds by two step mechanism as discussed in Sandmeyers reaction.

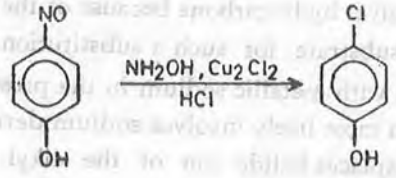
Sandmeyer Reaction :

The reaction is carried out by adding a solution of diazonium salt to a solution of hydrochloric acid and cuprous chloride with cuprous bromide or cuprous cyanide and the corresponding bromo or cyano aryl compounds are prepared. Other nucleophilic groups like $\bar{N}O_2$, $\bar{S}H$, N_3, $\bar{S}CH_3$, F and H_2ASO_3 replace the diazo group from the aromatic diazo substrate under the reaction condition. The reaction follows first-order kinetics with respect to both the diazonium ion and cuprous chloride solution. The $\bar{C}UCl_2$ ion probably coordinates with the diazonium cation involving copper and the terminal nitrogen of the diazo group to form a complex which is decomposed rapidly to an aryl radical by redox transfer process by the copper.

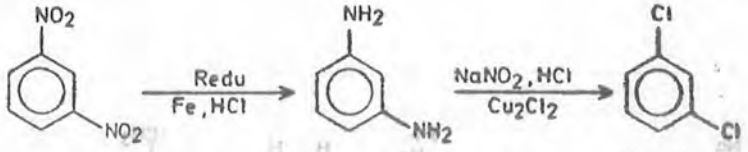


In p-nitrosophenols, the strongly electron-attracting nitroso group is easily displaced by chlorine when reacted with hydroxylamine in the presence of

cuprous chloride in hydrochloric acid. The modified procedure gives better percent yield of the halogen substituted phenol.

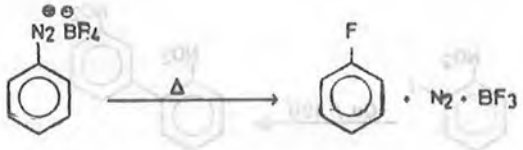


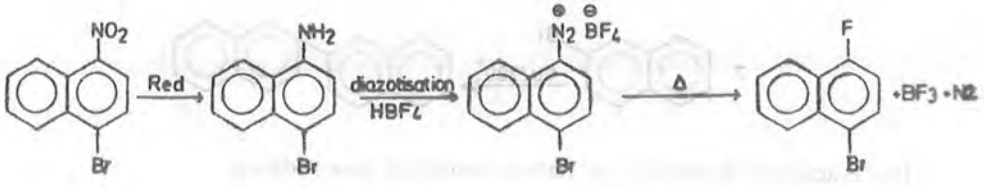
Generally m-dichlorobenzene is not easy to prepared but Sandmeyer method is convenient for such a synthesis as can be seen from double diazotisation of 1,3-dinitrobenzene.



Schiemann Reaction :

The reaction is used for replacing diazonium salt group with fluorine by adding fluoroboric acid to the diazotised amine in a distillation unit with a trap for borontrifluoride. The resulting diazonium fluoroborate is precipitated dried and thermally decomposed to give aryl fluoride. The product is collected after distillation.



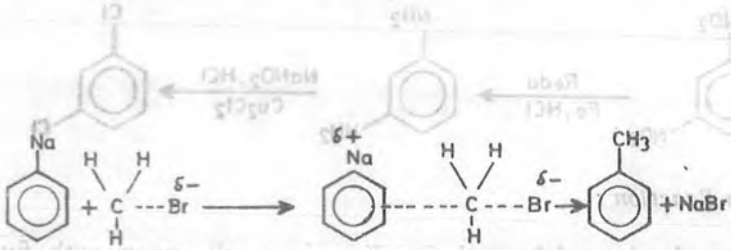


Wurtz-Fittig Reaction

Aryl halides do not undergo Wurtz reaction as alkyl halides do with metallic sodium to give hydrocarbons because of the absence of activating groups in the aryl substrate for such a substitution reaction. However, aryl halides do react with metallic sodium in the presence of primary alkyl halides. The reaction most likely involves sodium derivatives of the halides in which aryl anion displaces halide ion of the alkyl halide by aliphatic SN_2 process.

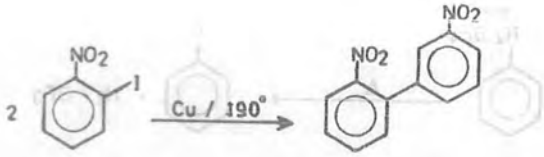
$$C_6H_5Br + CH_3Br \xrightarrow{Na} C_6H_5Na + CH_3Na + 2NaBr$$

$$C_6H_5Na + CH_3Na \not\longrightarrow C_6H_5CH_3 + 2Na$$



Ullman Reaction

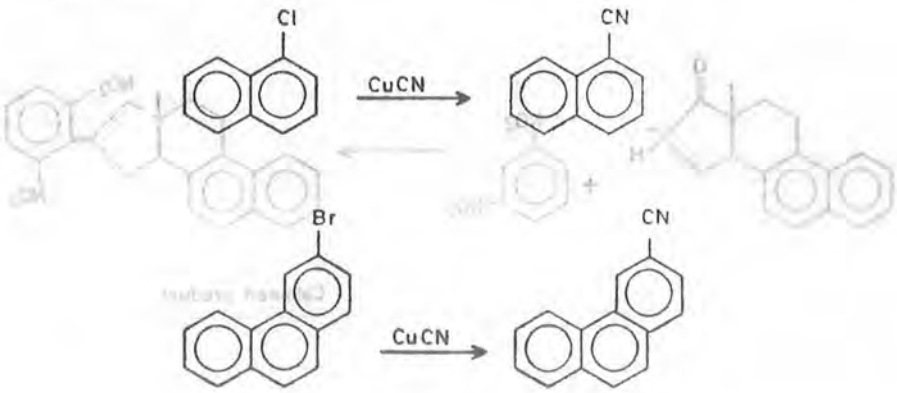
Symmetrical biphenyls may be synthesised by heating aryl halides with copper or silver powder with the exception of fluoroaryls. Iodo-and activated chloro-and bromo aryls are generally employed to get good yields of the racemic biphenyls.

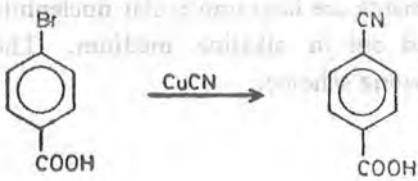


The reaction is homolytic in nature involving free radicals.

Rosemund-von Braun Reaction :

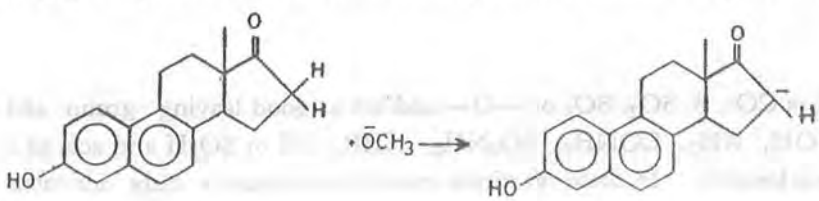
The reaction is useful for preparing aryl cyanide from aryl halides and cuprous cyanide in the presence of bases like pyridine or quinoline in excellent yields.



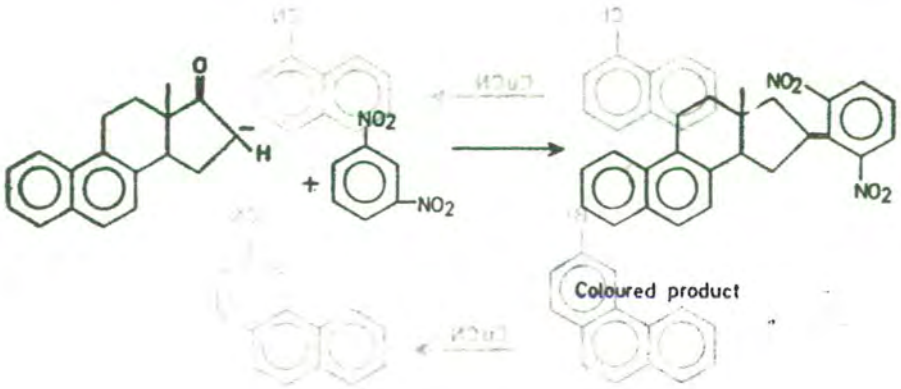


Ziemmernan Reaction :

It is widely employed as a bio-analytical procedure for the estimation of 17-ketosteroids. The analytical method involves the treatment of the steroidal compound with meta dinitrobenzene in ethoxide or methoxide ion. The base removes a hydrogen from the general structure—CO—CH_2— resulting a carbanion. The ketone carbanion attacks on the m-dinitrobenzene and displaces a hydride ion with the formation of highly coloured conjugated product. The coloured compound is estimated by a colorimeter.



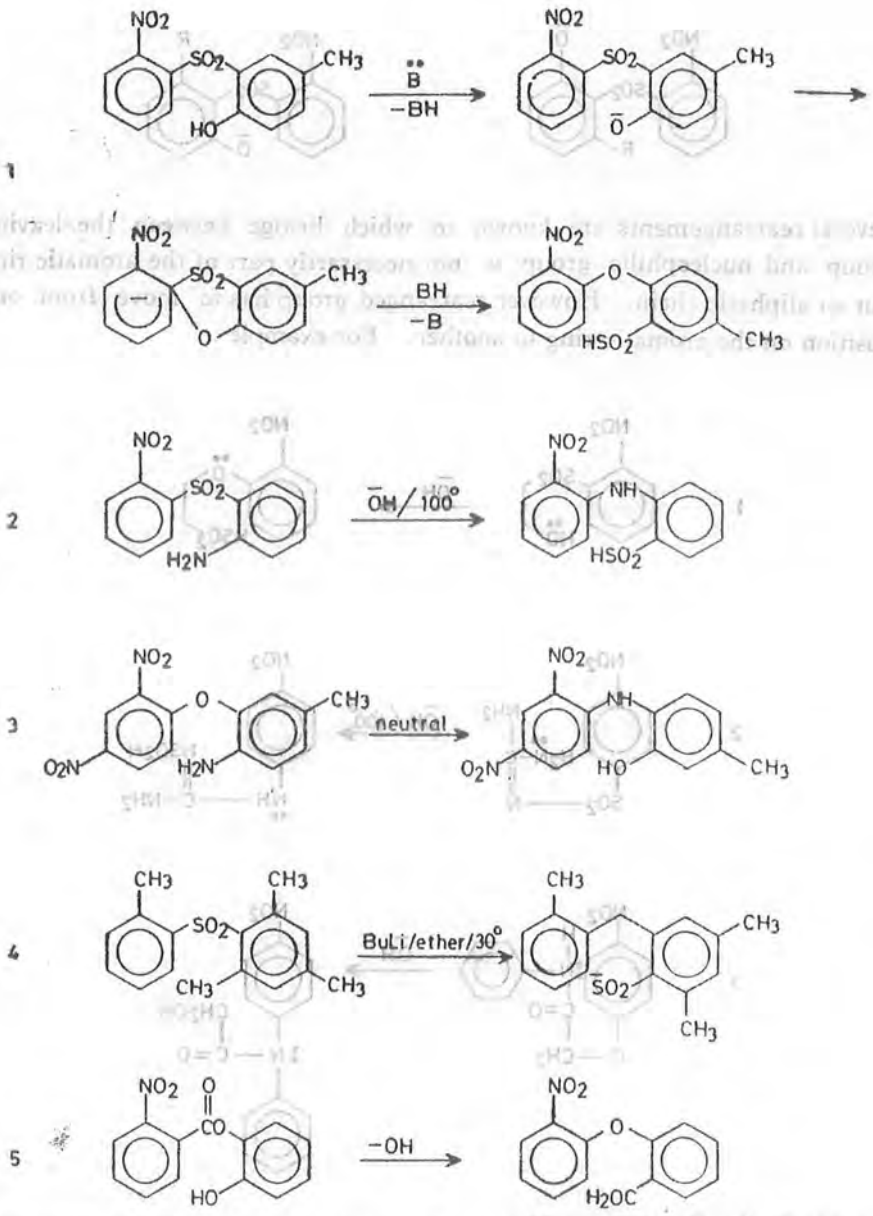
Equilenin



Smiles Rearrangement :

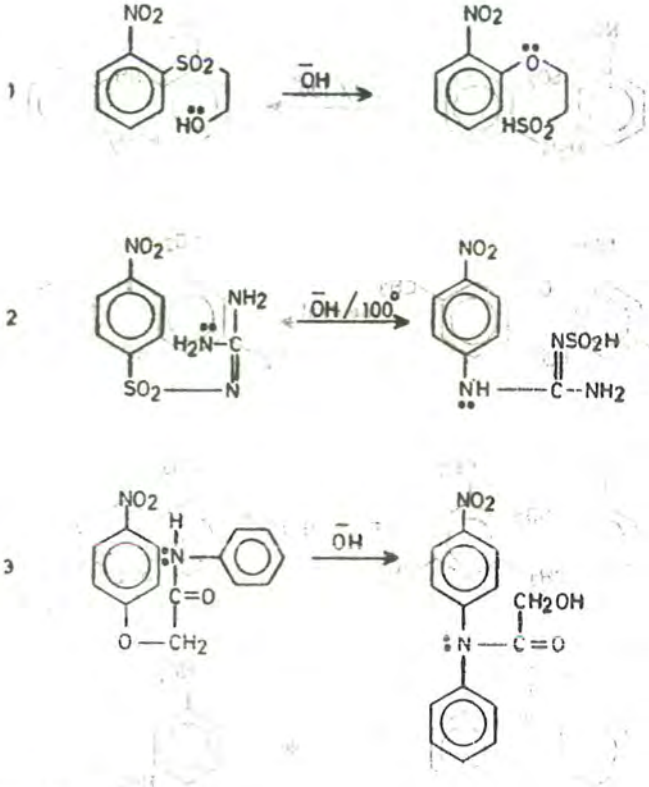
These rearrangements are interamolecular nuclephilic aromatic substitutions and are carried out in alkaline medium. They are represented generally by the following scheme.

where X is CO_2^-, S, SO_2, SO_3^- or —O— and act as good leaving group and YH is OH, NH_2, $CONH_2$, SO_2NH_2, NHR, SH or SO_2H and acts as a strong nucleophile. In these reactions aromatic substrate is duly activated by an electron withdrawing group such as nitro substituent. Typical rearrangements are presented below :



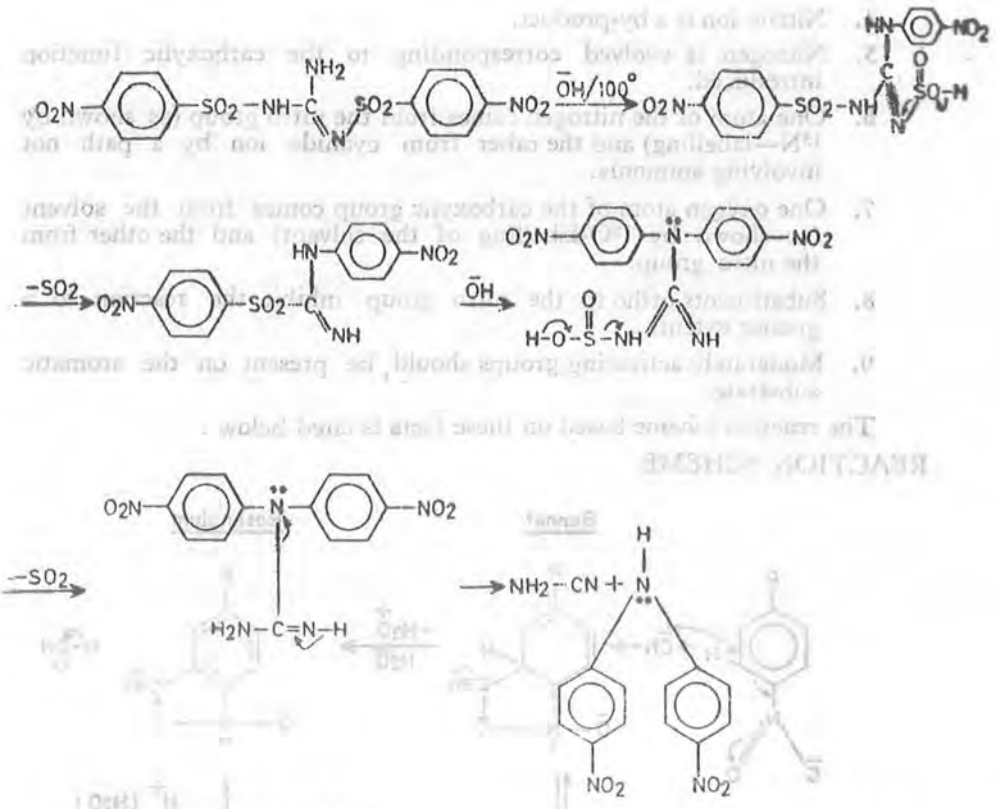
These rearrangements are accompanied by colour changes from red to yellow and are proposed to involve Meisenheimer type complexes. The substituents on the aromatic ring play important role in controlling conformations and favour the one which will exert the least energy of activation and steric interaction between the substituent and the nitro group of the aromatic ring.

Several rearrangements are known in which bridge between the leaving group and nucleophilic group is not necessarily part of the aromatic ring but an aliphatic chain. However rearranged group has to move from one position on the aromatic ring to another. For example :



Double Smiles Rearrangement :

For preparing high purity nitrated diphenylamine from urea or gaunidine the substrate is first treated with p-nitrobenzenesulphonyl chloride to give bis-(p-nitrobenzene-sulphonyl)-urea or-gaunidine. It is then treated with alkali at an elevated temperature. The reaction undergo double smiles rearrangement.



von-Ritcher Rearrangement :

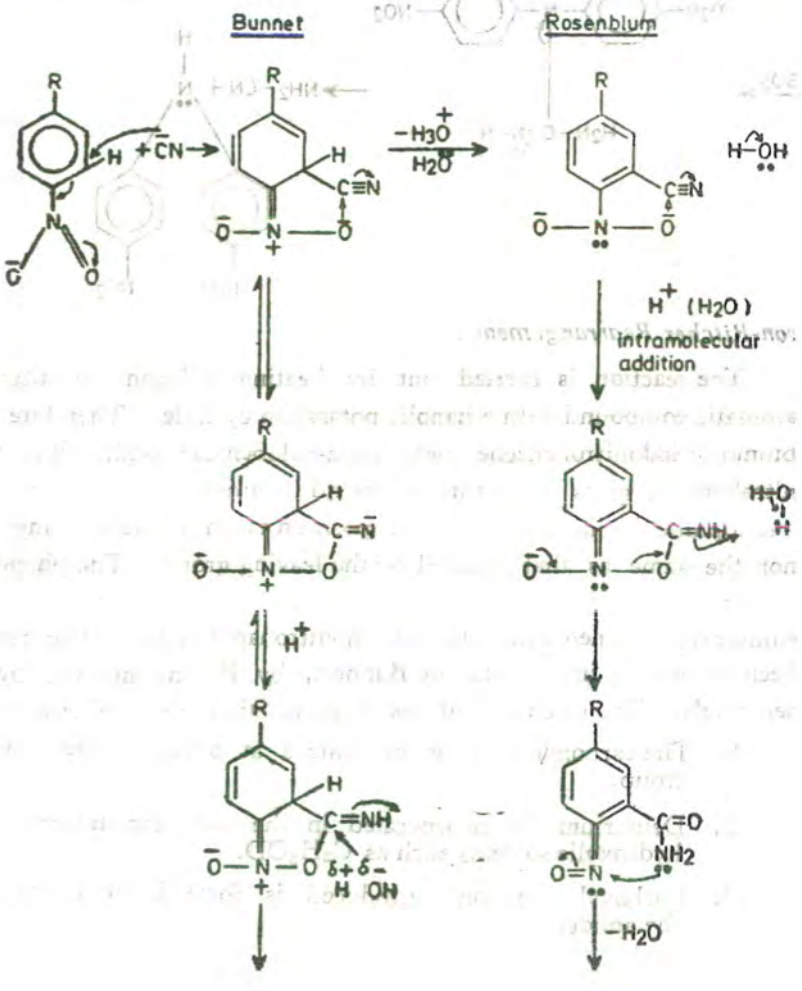
The reaction is carried out by heating halogen substituted nitro aromatic compound with ethanolic potassium cyanide. Therefore p-chloro, bromo-or iodonitrobenzene yield meta-halobenzoic acid, while m-bromo-nitrobenzene gives a mixture of o-and p-bromobenzoic acids. In these nucleophilic displacement reactions position taken by the entering group is not the same as that vacated by the leaving group. The phenomenon is also known as cine-substitution. The other nitro aromatics undergoing similar displacements include, dibromonitronaphthalene. The reaction has been extensively investigated by Bunnett, by Rosenblum and by Ullman separately. The essential features of the reaction are as follows :—

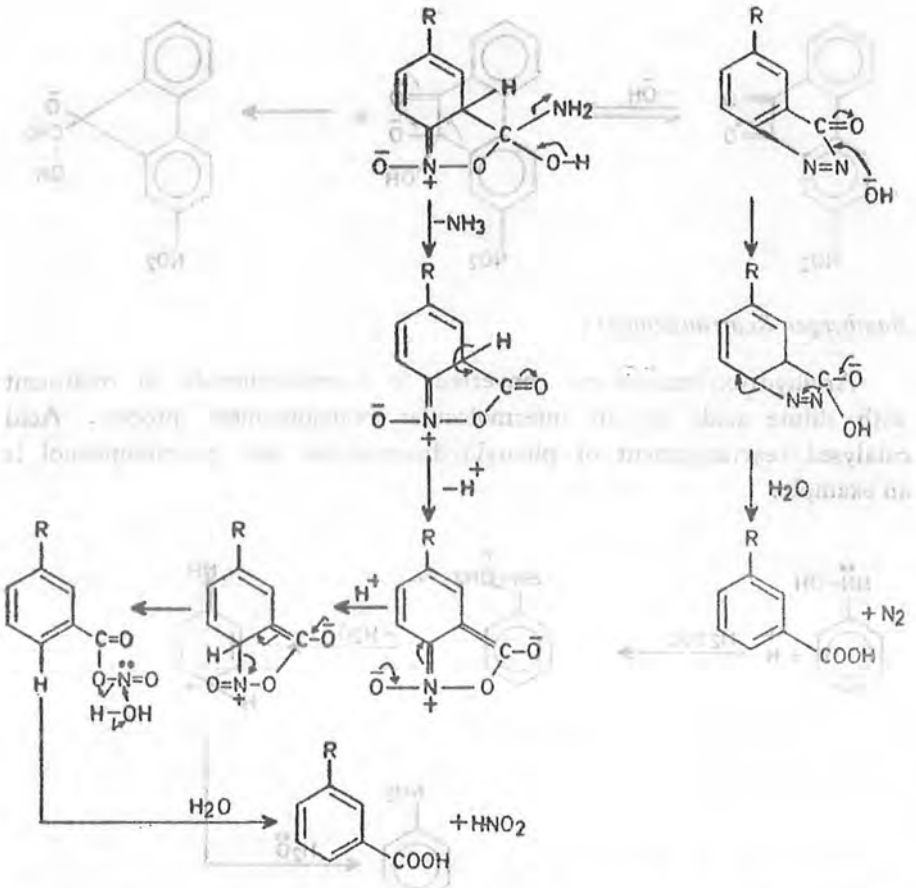
1. The carboxyl group is introduced at ortho to the leaving nitro group.
2. Deuterium is incorporated in the aromatic nucleus from the hydroxylic solvents such as C_2H_5OD.
3. Carboxyl function introduced is formed from the nitrile or the amide.

4. Nitrite ion is a by-product.
5. Nitrogen is evolved corresponding to the carboxylic function introduced.
6. One atom of the nitrogen comes from the nitro group (as shown by ^{15}N—labelling) and the other from cyanide ion by a path not involving ammonia.
7. One oxygen atom of the carboxylic group comes from the solvent (as shown by ^{18}O-labelling of the solvent) and the other from the nitro group.
8. Substituents ortho to the nitro group inhibit the reaction to a greater extent.
9. Moderately activating groups should be present on the aromatic substrate.

The reaction scheme based on these facts is cited below :

REACTION SCHEME

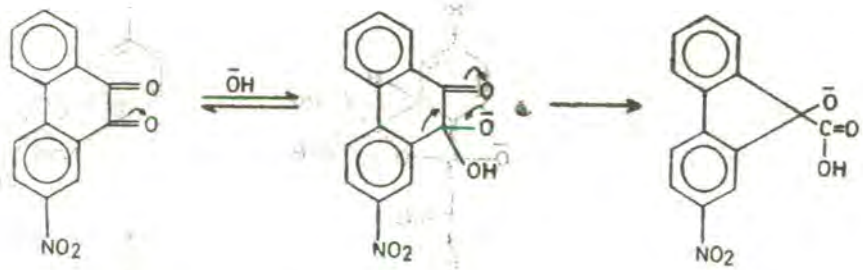




However experimental findings are in agreement with the reaction mechanism proposed by Rosenblum. The scheme proposed by Bunnet can not be ruled out because it is valid to certain extent and is the only mechanism which accounts for the nitrite ion formed in the reaction.

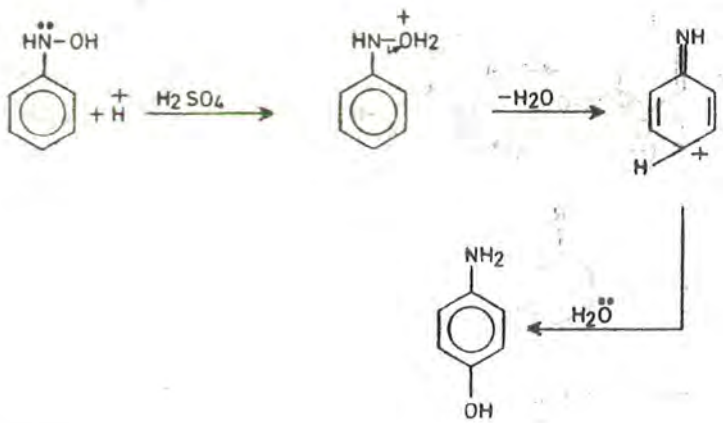
Benzilic Rearrangement :

In moderately alkaline medium nitrophenanthrene diquinones are rearranged by proton transfer to α-hydroxy acids like benzil. The reaction is an aromatic substitution because of the keto-function which become part of aromatic phenanthrene structure. Nitro group activates the aromatic substrate at the carbonyl carbon and attack by hydroxide group becomes facile. Absence of mesomeric effect with the nitro substituent through the aromatic ring facilitate the rearrangement.



Bamberger Rearrangement :

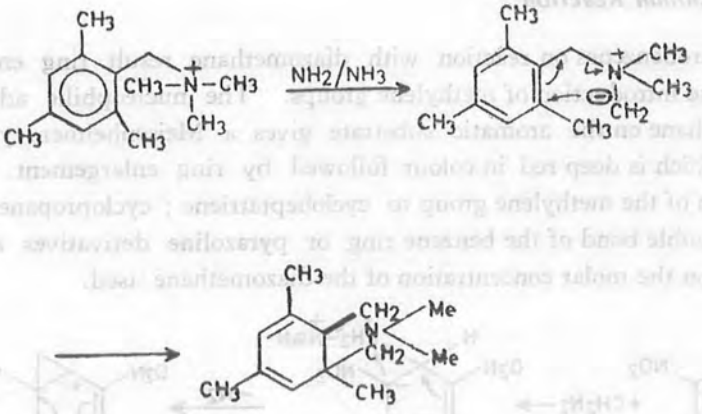
Arylhydroxylamines are converted to p-aminophenols on treatment with dilute acids by an intermolecular rearrangement process. Acid catalysed rearrangement of phenylhydroxylamine into p-aminophenol is an example.



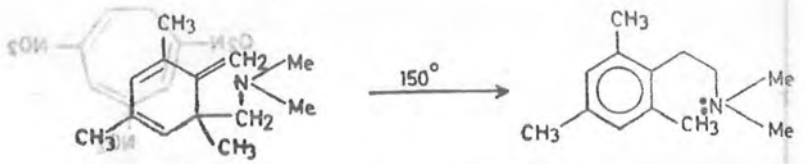
The mechanism proposed above is a unimolecular one. Bimolecular mechanism is also feasable in which removal of water and addition of the nucleophile are synchronous.

Sommelet-Hauser Rearrangement :

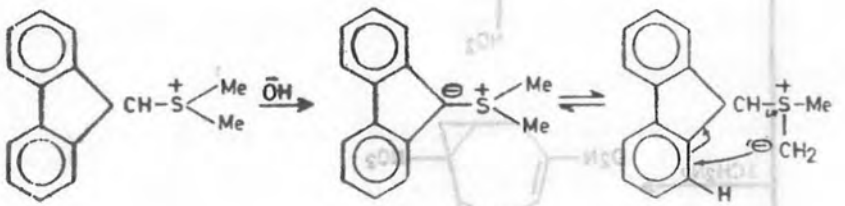
It is an internal nucleophilic aromatic substitution carried out by treating arylalkylammonium salts with a strong nucleophilic base in ammonia. Thus benzyltrimethylammonium salt on treatment with sodamide in ammonia removes an α-hydrogen of a methyl group resulting a carbanion which then attacks on the aromatic ring to give an exomethylene derivative which is isolable.

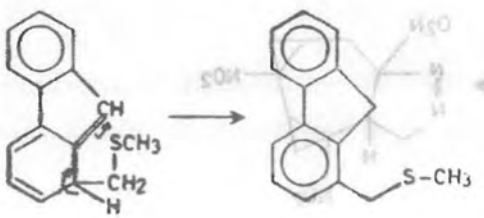


By simply heating the exomethylene product, tertiary arylalkyl amines are produced with the introduction of a methylene group and rearomatisation.



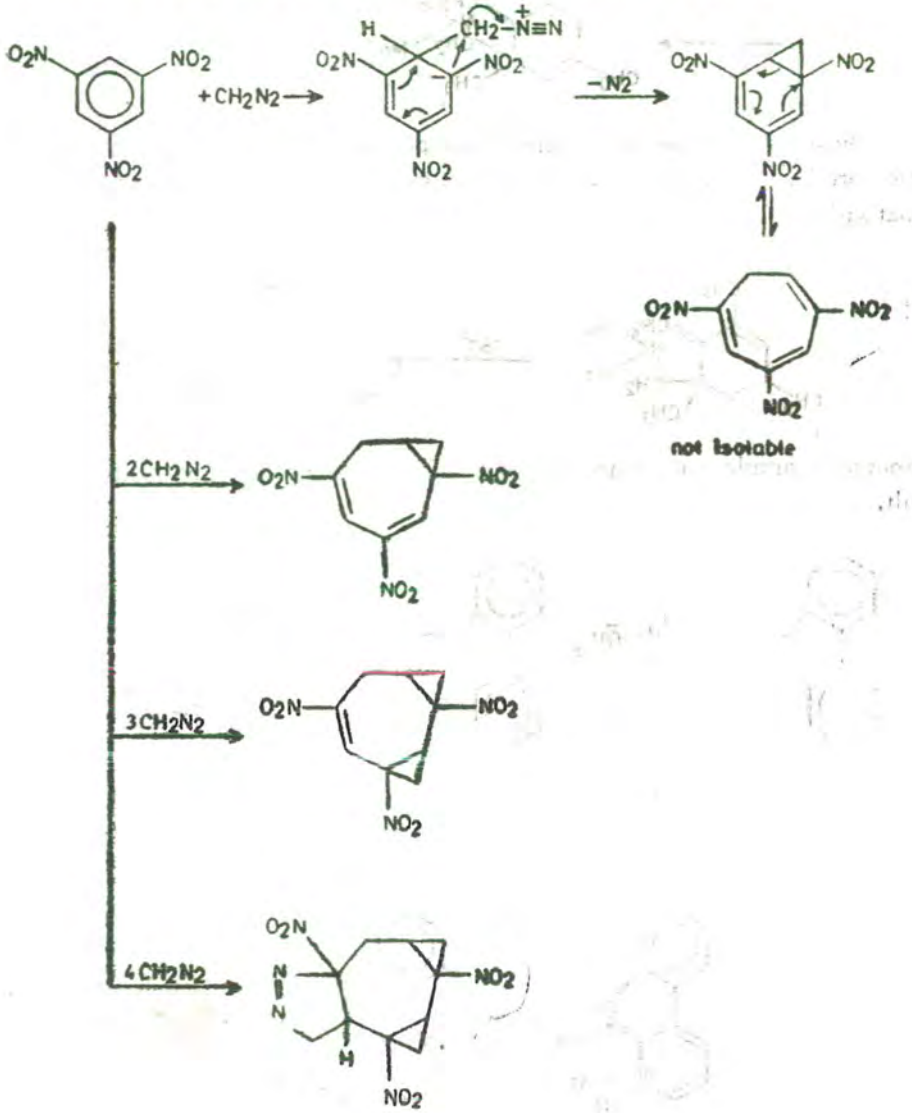
Another example is the rearrangement of 9-Fluorenyldimethyl sulphonium salt.





Heinke-Pechman Reaction :

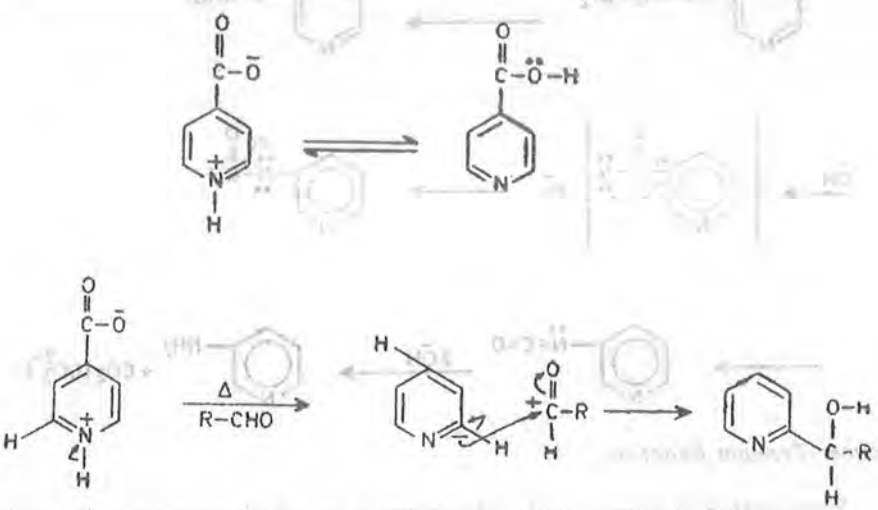
Polynitrobenzenes on reaction with diazomethane result ring enlargements by the introduction of methylene groups. The nucleophilic addition of diazomethane on the aromatic substrate gives a Meisenheimer type of complex, which is deep red in colour followed by ring enlargement. The introduction of the methylene group to cycloheptatriene ; cyclopropane ring along the double bond of the benzene ring or pyrazoline derivatives are all dependent on the molar concentration of the diazomethane used.



Trinitrotoluene, picryl chloride, picric acetate and trinitro xylene react with diazomethane to give ring enlargement products. More reactive diazoalkanes, give mainly pyrazolines.

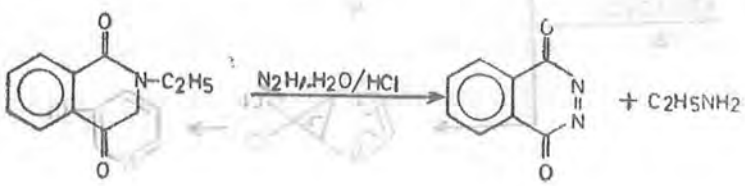
Hammick Reaction :

In six-membered heteroaromatic rings the reactivity is dependent on the heteroatom influence and is relatively small when a substituent is present at β-position to the heteroatom than at α- and γ-positions, where the effect is large. For instance, α-, β- and γ-pyridine carboxylic acids are decomposed on heating in the order $\alpha > \gamma > > \beta$ and can be explained due to the inductive stabilisation of the intermediate ion formed. In this reaction pyridine carboxylic acid is heated in the presence of aldehydes or ketones and α-substituted amino-methanol are prepared. The reaction sequence is as follows :



Ing-manske Reaction :

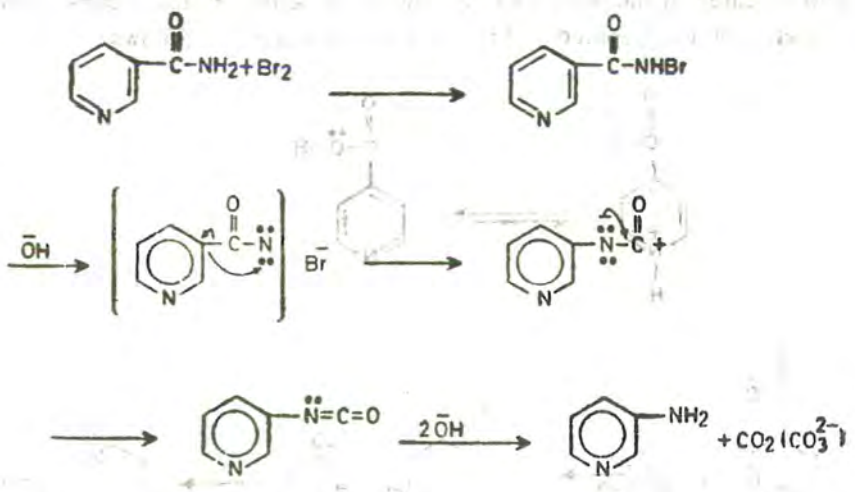
When N-substituted imides are condensed with hydrazine, primary amine and azodienes are produced. For instance, heating N-alkylphthalimide gives 1,4-phthalazinedione and an alkylamine when treated with hydrazine hydrate in acidic medium.



Equivalent amounts of hydrazine and imide are refluxed in alcohol for some time. The solid product obtained is then separated from alcohol and heated with hydrochloric acid in such a way that steam passes through the reaction mixture. The precipitated final product is separated and filtered off. The filtrate contains the amine-hydrochloride salt and gives a very good yield of the primary amine.

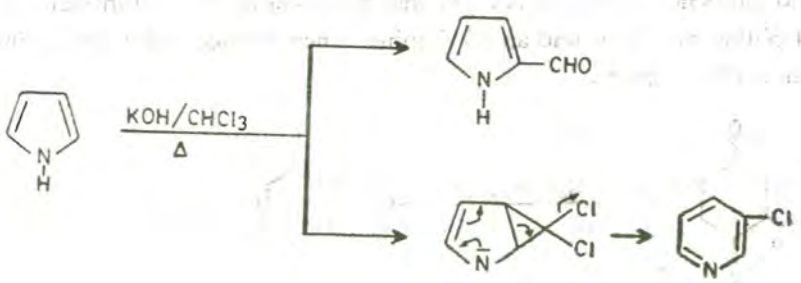
Hofmann Rearrangement :

3-Aminopyridine is prepared by treating nicotinamide with bromine in alkaline medium. The transformation involves the formation of a C-N bond between the heterocyclic carbon and nitrogen of the amide group .



Reimer-Temann Reaction :

Formylation of pyrrole with chloroform in an alkaline solution is easily achieved by heating the reaction mixture. 2-Pyrrole-carboxaldehyde is produced along with a ring enlargement product 3-chloropyridine.

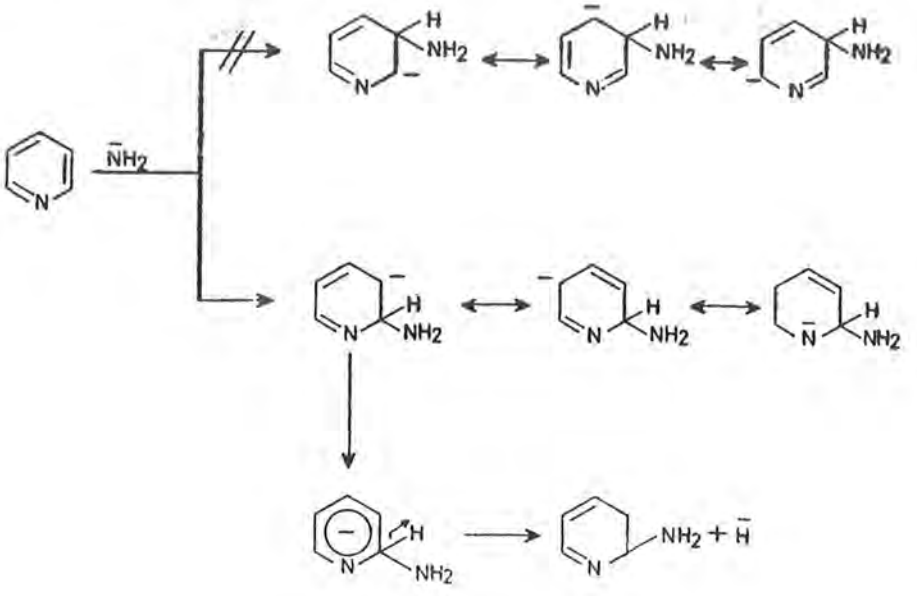


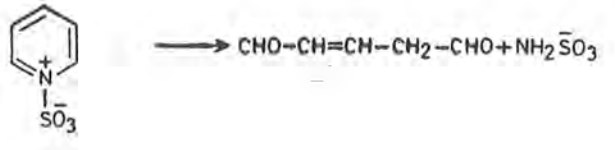
Zinke Reaction.

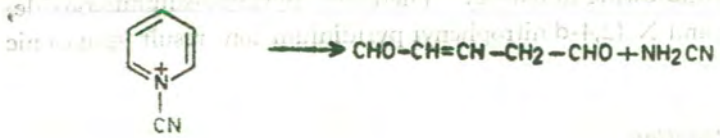
Primary amines on reaction with substituted pyrylium cations or pyridinium salts result open chain dialdehydes. The substituents on nitrogen are strong electron-withdrawing in nature. Therefore pyridine-sulphurtrioxide; N-cyanopyridine and N-(2,4-dinitrophenyl pyridinium ion result glutaconic dialdehyde.

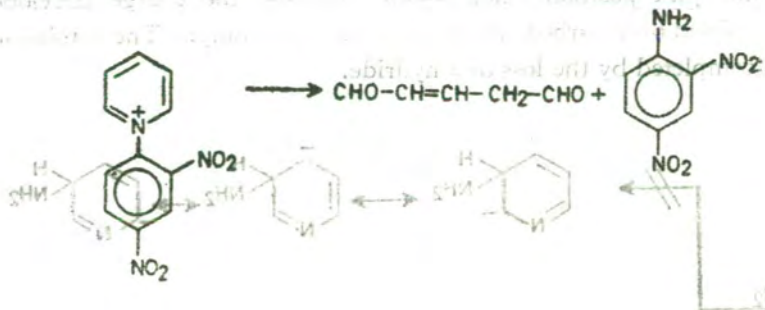
Tschitchibabin Reaction :

2-Aminopyridine is prepared by heating pyridine with sodamide. 2-position of the pyridine is aminated because the charge developed by the addition of the amide ion on the ring partially resides on nitrogen. A similar addition at 3-position is not possible because the charge developed is only delocalised over carbon atoms of the ring only. The amination reaction is completed by the loss of a hydride.






CHO–CH=CH–CH2–CHO + NH2CN
CN


CHO–CH=CH–CH2–CHO +
NH2
NO2
NO2
NO2

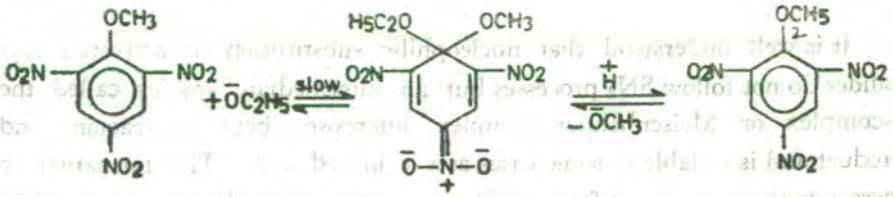
MEISENHEIMER COMPLEXES

It is well understood that nucleophilic substitution of activated aryl halides do not follow SN_2 processes but an intermediate species called the σ-complex or Meisenheimer complex interposes between reactant and product and is isolable in some cases as a coloured salt. The formation of these complexes is known for over 90 years and particularly by the covalent adduct of dinitroaromatic ethers along with their structural representation where cyclohexadienide structure involves all the nitro groups for charge delocalisation. The carbon undergoing displacement becomes sp^3 hybridised and the negative charge is produced as a result of the covalent bonding by the incomming nudeophile. The aromatic substrate is stabilised over the aromatic system which is activated by an electron-withdrawing group such as a nitro group substituted at 2- and 4-position of the benzene ring.

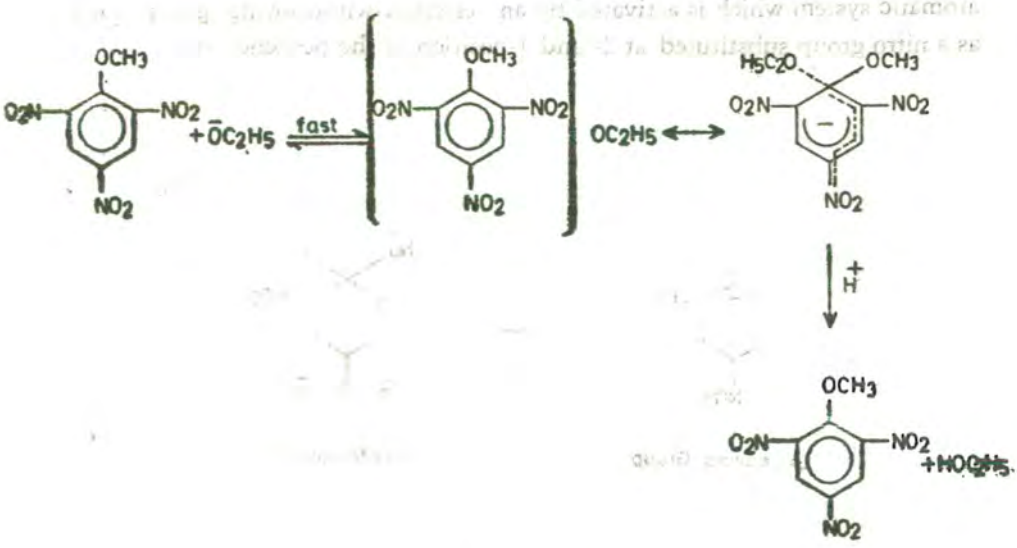
L = Leaving Group Nu = Nucleophile

Several studies in this field have demonstrated that along with the σ-complexes some π-complexes (charge-transfer complexes) are also produced in the aromatic nucleophilic displacement reactions. For example. the

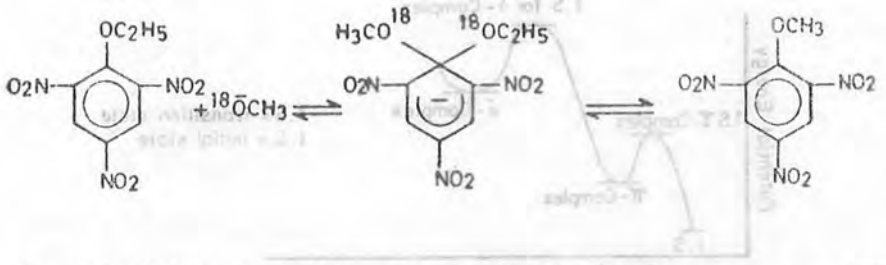
reaction of 2,4,6-trinitroanisole with ethoxide ion reveals that both slow and fast reactions occur corresponding to and σ-complexes and are evidenced by the fact that in slow reaction the intermediate complex is decomposed by dilute sulphuric acid to 2,4,6-trinitrophenotole while undissociated acids emplo yed do not decompose the intermediate complex.



However charge-transfer complexes if present are known to decompose readily by general acid catalysis reversibly to the reactants because these complexes are produced as a result of the fast reaction between the donor and the acceptor.



The product of the slow reaction which is regarded as the σ-complex is identified by NMR, Visible, UV and IR spectra and is also prepared from the reaction of 2,4,6-trinitrophenetole with methoxide ion. The use of the radio-active 18-OCH_3 ion confirmed the view point further when the product obtained was

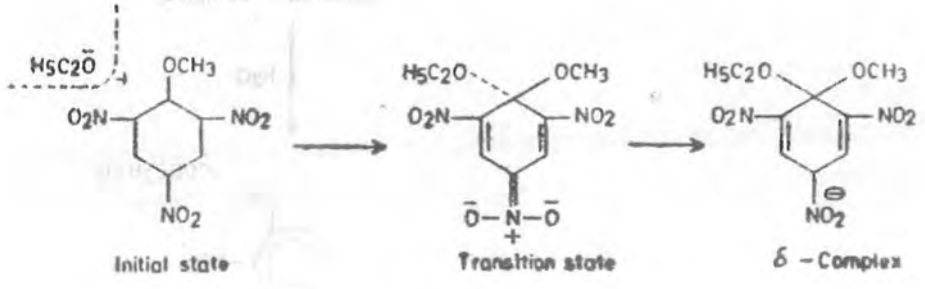


from2,4,6-hrinitrophenetole. Kinetics of slow and fastreactions at -80° in excess of ethoxide ion are indicative of the σ-andπ-complex. (Table).

TABLE

Reaction of 2,4,6 trinitroanisole with $\bar{O}C_2H_5$ at -80°	π - Complex	δ - Complex
$\log_{10}K_1$	1.09 l/mole/sec	-4.81 l/mole/sec
$\Delta E^{\neq}$	10.4 kcals/mole	13.7 kcal/mole

Where $\log_{10}k$ is the rate constant for the forward reaction and $\triangle E$ is the free energy of the reaction. Thus it is evident that in the formation of σ-complexes, charge-transfer complexes are also followed. The preliminary formation of the π-complexes on route to the σ-complexes do not change the activation energy of the reaction because activation energy is the energy difference between the initial state and the transition state leading to the formation of the σ-complex.



This is illustrated below in the energy profile (fig.)

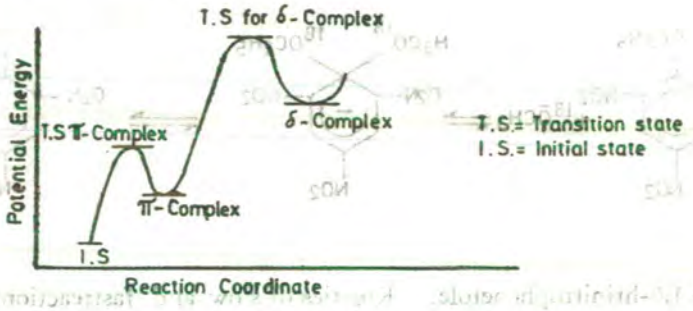
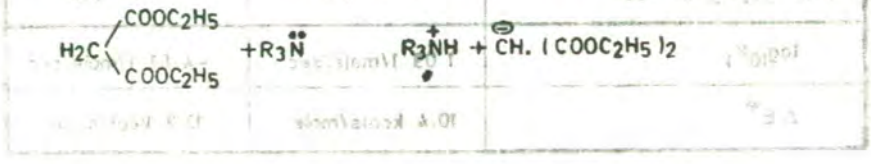
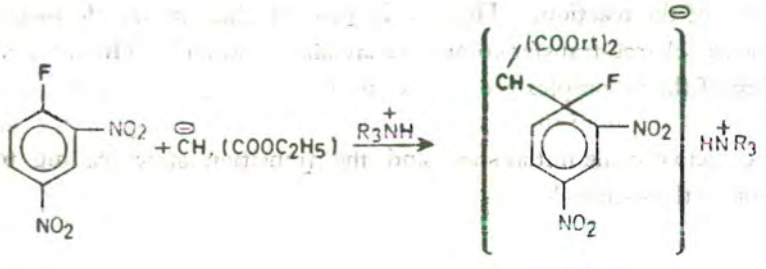


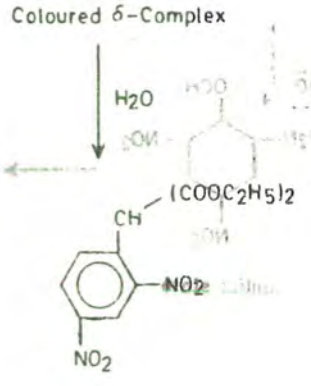
FIG. Energy profile showing π-Complex and δ-Complex formation

The interaction of 1-fluoro-2,4-dinitrobenzene and ethylmalonate in the presence of triethylamine results a coloured solution which is stable in dimethylformamide. However on addition of water decolonisation occurs and 2,4-dinitrophenylmalonate ester is produced. The coloured product is considered as the triethylammonium salt of the σ-complex.

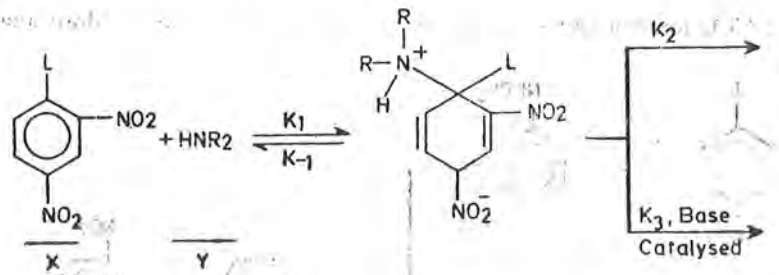




Coloured δ-Complex



Kinetic investigations reveal the presence of σ-complex in nucleophilic aromatic substitution and are demonstrated in a model system involving secondary amines and 2,4-dinitro aryl derivatives which is base catalysed. The σ-complex formed is such that the loss of proton from the ammonium part and the expulsion of the leaving group (L) are more favourable rather than the elimination of $R\bar{N}R$ ion from the complex which is itself a poor leaving group. Hence the model provides for a lower activation process for the conversion of σ-complex to the products.



Steady-state treatment of the above process reveals the expression

$$\frac{\text{Rate}}{[x][y]} = K = \frac{K_1K_2+K_1K_3[B]}{K_{-1}+K_2+K_3[B]}$$

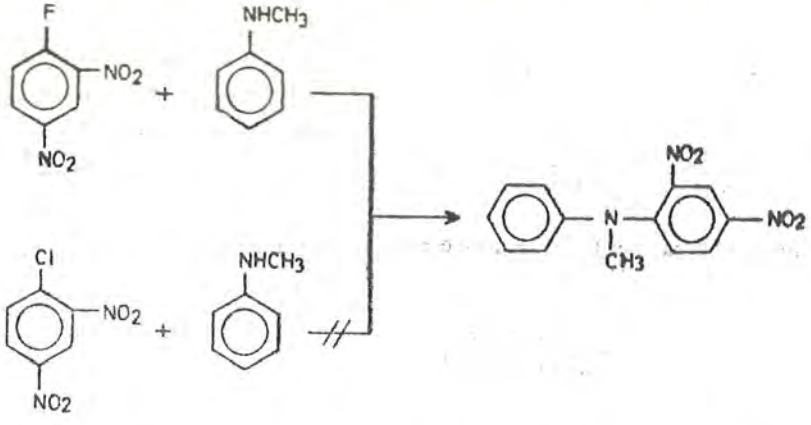
It is obvious that two competing paths are involved for the conversion of the σ-complex into product: one is uncatalysed process and the second base-catalysed, where the nature of the base is a Bronsted type such as R_2NH, $RCO^{-}{}_2$, $O\bar{H}$. The steady-state approximation further reveals that for a forward reaction i.e. the conversion of σ-complex into the products, the rate constant becomes.

$$k = k_{-1}.$$

However when the back-ward process is too slow in relation to the forward reaction i.e. K-I < K2 + K3 [B].

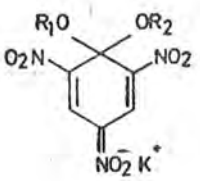
Such a situation is indicative of the formation of the σ-complex at a rate-determining step. However if the backward reaction is fast enough to compete with the forward reaction i.e. K-1 > K2 + K3 [B], the rate-determining step is the product formation step and here base catalysis would be expected. Therefore the forward reaction would be followed for the systems

containing poor leaving groups i.e. when L=F rather than when L=Cl. However when backward and forward reactions are in equilibrium i.e. K—1=K2, then base catalysis is observed at very low concentrations of the Bronsted base but the catalytic effect of the base will decrease when the concentration of the base is increased. For example base catalysis is more effective in the reaction of 1-fluoro-2,4-dinitrobenzene with Bronsted bases than with 1-chloro-2, 4-dinitrobenzene. Very convincing systems are those of 1-fluoro-2, 4-dinitrobenzene with N-methylaniline catalysed by $O\overline{H}$ ion or $CH_3C\overline{O}2$ ion but this catalysis is virtually absent with chloro-analogue.

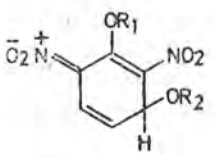


The detailed chemistry and the structural characteristics of stable σ-complexes had been developed by the systematic study of visible, IR and NMR spectroscopy as well as thermodynamic study of the coloured products formed from the interaction of picryl ethers and potassium alkoxide. Large number of evidences were provided by isolating the same product from 2,4,6-trinitroanisole and potassium ethoxide and from 2,4,6-trinitrophenetole and potassium methoxide. A quinoid structure (I) was proposed for the product obtained from both the interactions. Such addition complexes are reported to be formed from a large variety of necleophiles with electron deficient aromatic compounds and are called Meisenheimer or Jackson-Meisenheimer complexes (σ-complexes). The crystal structural determinations provided the conclusive evidence for the structure (I) ($R_1 = R_2 = CH_2$ CH, $R_1 = R_2 = CH_3$). Instead of quinoid structure another structure (II) has also been suggested. Molecular orbital calculations and crystal staucture determinations indicated that most of the negative charge localised on the nitro group para to the Sp^3 ring carbon. Thus structure (I) was considered

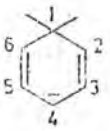
more suitable where as the complexes with substituents other than nitrogroup, para to SP^3 ring carbon could be represented like structure (II).



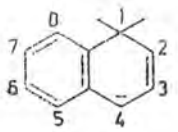
I



II



III



IV

In benzene and naphthalene complexes Sp^3 ring carbon was considered C-1 and proceed to right as in the canonical forms III and IV. Substitution on the anionic ring of complexes at a position other than C-1 was termed as "substituted cyclohexadienate". Structure (1) ($R_1=R_2=H_3$) was suggested to be prefered by the evidences from visible and infra-red spectroscopy alongwith NMR studies.

REFERENCES

1. E.S. Gould Mechanism and Structure in Organic Chemistry, Holt, Reinhhart and Winston, New York, 1965.
2. J.F. Bunnett, Mechanism and Reactivity in Aromatic Nucleophilic Substitution, Quarterly Reviews, 1958, 12,1.
3. R.O.C Norman, Principles of Organic Synthesis, Methuen and Co. Ltd., London, 1968.
4. T.A. Geissman, Principles of Organic Chemistry, 3rd edi., W.H. Freemon and Co., San Franciso, 1968.
5. O. Reuto V. Theoretical Principles of Organic Chemistry, MIR Publishers, Mosco, 1970.
6. M.H. Palmer, The Structure and Reactions of Heterocyclic Compounds, Edward Arnold (Publishers) Ltd., London, 1967.
7. E. Ochiai, Aromatic Amine Oxides, Elsevier Publishing Co., New York, 1967.
8. L.M. Stock, Aromatic Substitution Reactions, Precentic-Hall, Inc., New Jersey, 1968.
9. G.M. Badger, The Chemistry of Heterocyclic Compounds, Academic Press, New York, 1961.
10. A.R. Katritsky and J.M. Lagowski, The Principles of Heteroyclic Chemistry, Methuen and Co., Ltd., London, 1967.
11. J. Miller, Aromatic Nucleophilic Substitution, Elsevier Publishing Co., New York, 1968.
12. C.K. Ingold, Structure and Mechanism in Organic Chemistry, Corner University Press, 1953.
13. S.D. Ross, Progress in Physical Organic Chemistry, Vol. I, Interscience Publishers, New York, 1963.
14. A.R. Surrey, Name Reactions in Organic Chemistry, 2nd, ed., Academic Press, New York, 1961.
15. J.F. Bunnett, and R.E. Zahler, Cheem. Rev. 49, 275, 1951.

16. A. Streitwieser, Molecular Orbital Theory for Organic Chemistry, John Wiley, New York, 1961.

17. B.C. Challis, Ann. Rep. Progr. Chem., Chem., Soc., London, 62, 263, 1965.

18. H. Heaney, Chem. Rev. 62, 81, 1962.

19. J.R. Knowles, R O.C. Norman and J.H. Professor, Proc. Chem, Sec., 341, 1961.

20. L M. Stock and H C. Brown, Advances in Physical Organic Chemistry, Vol. I, Academic Press, New York, 1963.

21. P R., Wells, Chem. Rev , 63, 171, 1963.

22. J J. Lagowski, Quart. Rev., 13, 233, 1959.

23. G. Gilento, Chem. Rev., 60, 146, 1960,

24. R.G.R. Bacon and H.A. Hill, Quart. Rev., 19, 95, 1965.

25. R.A. Shaw, B.W. Fitzsimmons and B.C. Smith, Chem. Rev. 62, 247, 1962

26. N L. Paddock, Quart. Rev., 18, 168, 1966.

27. L W. Allen, J. Chem, Educ. 44, 38, 1967.

28. T. Nozoe, Progress in Organic Chemistry, Vol V, Butterworths, London, 1961.

29. A. Salam Mirza, M. Phil. Thesis, University of Islamabad, 1973.

UNIVERSITY OF ISLAMABAD PRESS

LIST OF PUBLICATIONS

1. **Alberuni's Indica :**

(A record of the Cultural History of South Asia about AD 1030) Abridged and Annotated by Prof. AHMED HASSAN DANI, Dean, Faculty of Social Sciences, University of Islamabad (Hard bound)

Price Pak. Rs 20.00
US $ 3.00

2. **Britain and Pakistan**

A study of British attitude towards the East Pakistan crisis of 1971, by Prof. K. K. AZIZ, Chairman, National Commission on Historical and Cultural Research.

Price Pak Rs. 35.00 (Hard bound)
Rs. 20.00 (Paper Back)

3. **Proceedings of the First Congress of Pakistan History and Culture :**

Vol. I Addresses, Proceeding and Papers on

(a) Muslim State and Society in the 18th Century.

(b) Social and Economic Institutions of the Muslims since 1858.

(c) Our Cultural Heritage.

Edited by Prof AHMAD HASSAN DANI (Under Print)

Vol. II Historical Writings on Pakistan : (Methodology and Inter-Pretation)

Edited by Prof. AHMAD HASSAN DANI Price Pak. Rs. 20.00
US $ 3.00
(Hard bound)

Vol. III Quest for Identity:

Edited by Dr. WAHEEDUZZAMAN,
Chairman, Department of History,
University of Islamabad. (Under Print)

4. **The British in India :**

A study in British Imperialism
by Prof. K K AZIZ (Under Print)

5. **Elementary Quantum Mechanics for Chemistry Students :**

by Dr. MAHBOOB MOHAMMAD,
Assistant Professor,
Department of Chemistry,
University of Islamabad. (Under Print)

6. **University Brochure :** Price Pak. Rs. 3.00

ORDERS :-

Manager Bookshop & Publication Cell,
University of Islamabad.
Islamabad (PAKISTAN)
Tele : 21028
Cable : UNIVERSITY

SCRUTINY

A bi-annual publication of International Forum, University of Islamabad. Includes articles written by eminent Pakistani and foreign writers covering wide range of subjects of international, cultural and historical significance to Pakistan. The January-June 1974 issue of 'Scrutiny' consists of 116 pages and includes the following articles :-

Some Reflections on Pakistan's Culture	ANNEMARIE SCHIMMEL
The Changing Structure of International Politics in South Asia	WAYNE WILCOX
Pakistan's Political Culture during Ayub Era	SHARIF AL MUJAHID
The Realities of Political Underdevelopment	LAWARENCE ZIRING
Elections, Army Rule and the Problem of Nation-Building in Pakistan	SALEEM M. M. QURESHI
England and the Arabs	NEVILL BARBOUR
A 1939 Scheme of Confederation for India	K. K. AZIZ
The Middle East War	A. B. AZIM

Annual Subscription : In Pakistan Rs. 15/-
For foreign countries
Shillings-8