Organic Chemistry-4

Semester-4, CBCS

Course: CEMA CC-4-8-TH

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Recommended texts:

1. Study Guide to Organic Chemistry, Volume 2, by Saha, Chakraborty, Saha & Basu, Techno World, ISBN 9788192669588,
2. Study Guide to Organic Chemistry, Volume 4, by Saha, Chakraborty, Saha & Basu, Techno World, ISBN 9788192695259,
3. Organic Chemistry, Second Ed. by Clayden, Greeves & Warren, OUP, ISBN 9780198728719
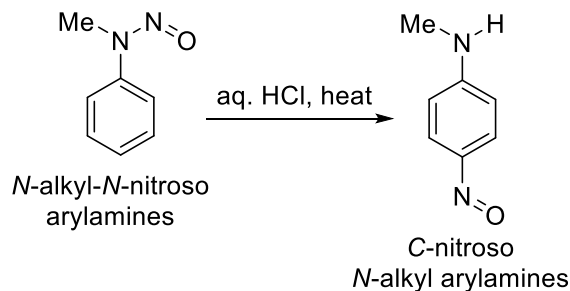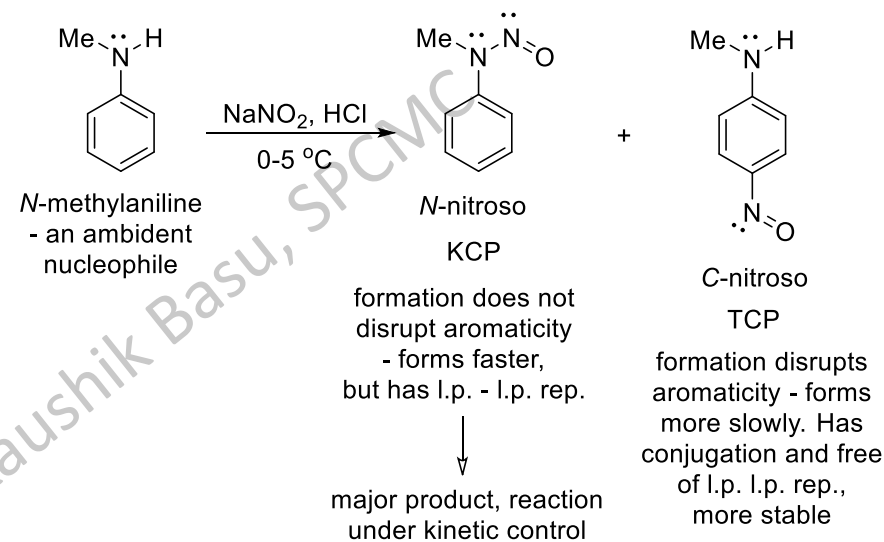
Rearrangements in Organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: Fischer-Hepp rearrangement

Transformation of an *N*-nitroso derivative of a secondary aromatic amine to the corresponding *p*-nitroso derivative, under the influence of acid.
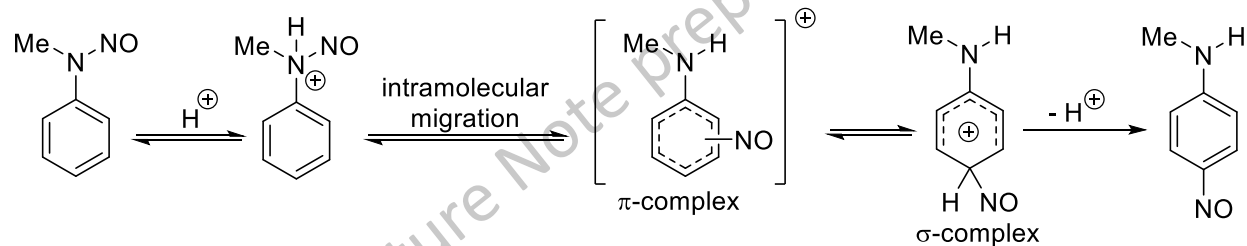
Background information:

Nitrosation of secondary aromatic amines like *N*-methylaniline gives a mixture of *N*-nitroso and *C*-nitroso dev. (compare acylation of phenol, as seen in Fries)

When the *N*-nitroso dev. is heated with aq. HCl, it is converted to the *C*-nitroso product. this is the Fischer-hepp rearrangement.

N-methylaniline
- an ambident
nucleophile

N-nitroso
KCP

formation does not disrupt aromaticity - forms faster, but has l.p. - l.p. rep.

↓

major product, reaction under kinetic control

C-nitroso
TCP

formation disrupts aromaticity - forms more slowly. Has conjugation and free of l.p. l.p. rep., more stable

N-alkyl-*N*-nitroso arylamines

aq. HCl, heat

C-nitroso
N-alkyl arylamines

Mechanism: Intramolecular migration of nitrosonium:

π-complex

σ-complex

Very similar to the intramolecular variant of the Fries rearrangement.

Proof of intramolecularity:

When the rearrnagement is carried out in presence of ^{15}N-enriched $NaNO_2$, there is no incorporation of radiolabelled N into the end-product.
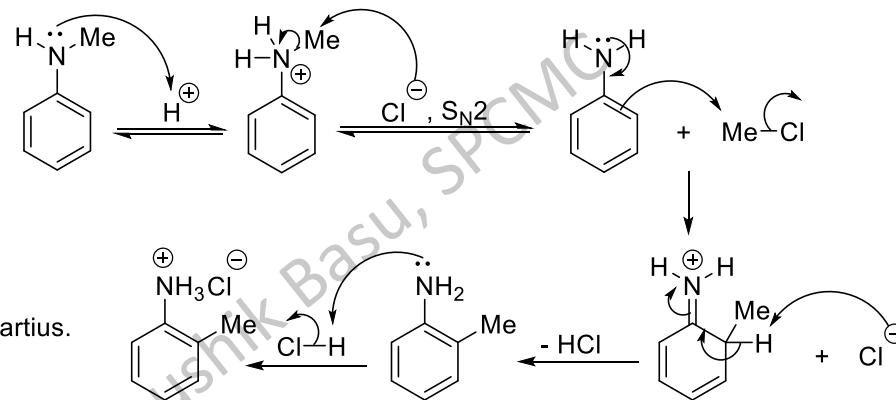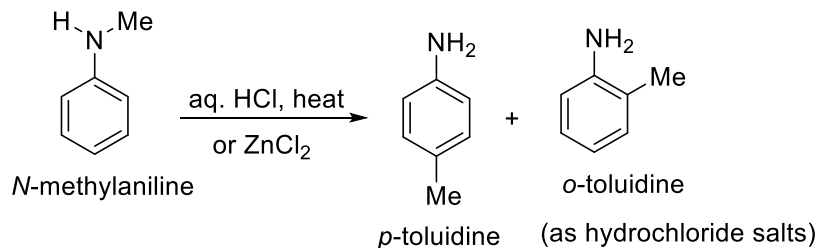
This proves that the migrating nitrosonium does not get detached from the starting material at any time and NO^+ from outside cannot enter.

Rearrangements in Organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: Hofmann-Martius rearrangement

Transformation of an *N*-alkyl derivative of an aromatic amine to the corresponding *C*-alkyl derivative, under the influence of acid. Alkyl group migrates to the *o*-/*p*-positions w.r.t. the N.
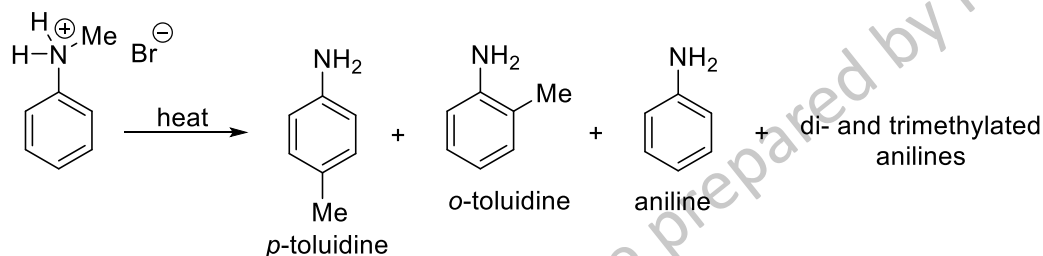
Mechanism: Intermolecular migration of alkyl

N-methylaniline

aq. HCl, heat or ZnCl₂

*p*-toluidine   *o*-toluidine

(as hydrochloride salts)

When a Lewis acid is used instead of a protic acid, the rearrangement is called Riley-Hickinbottom rearrangement; a variation of the Hofmann-Martius.

Proof:

1. Intermolecular nature proved by following experiment:

similarly, *p*-attack leads to the *p*-product

p-toluidine   *o*-toluidine   aniline   + di- and trimethylated anilines

The *in situ* formed MeBr reacts with aniline to afford the *o*- and *p*-toluidines. These arylamines may also react further with MeBr to produce di- or trialkylated products. As supply of MeBr is equal to that of aniline, some aniline will remain unreacted. If the reaction were intramolecular, we would have had only *o*- and *p*-toluidines

o-toluidine (already formed in the medium)   aniline   Me−Br   2,4-dimethylaniline   aniline
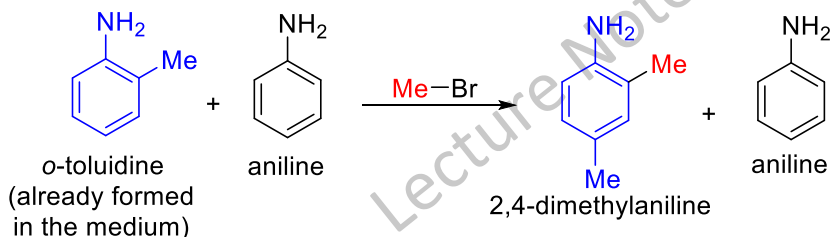
Unreacted aniline remains in the medium.

2. The *in situ* generated alkyl chlorides has been recovered from the medium, thereby proving their formation.

heat   aniline   + Me−Cl (isolated)
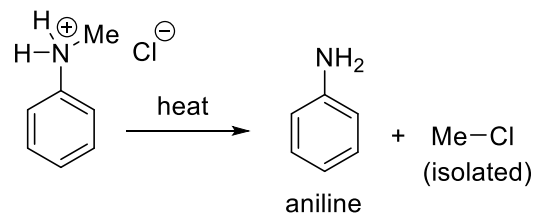
3. Bromide, chloride and iodide gave *different o-/p-* ratio under same reaction condition which proves that the halide ions are involved in the reaction, as per the mechanism proposed.

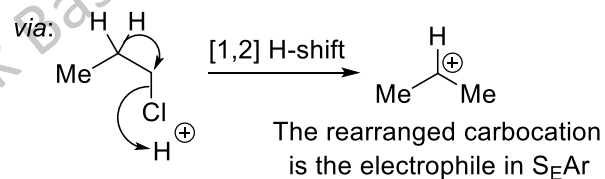# Rearrangements in Organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: Hofmann-Martius rearrangement

Proof:

4. The recovered primary organohalides do not show any rearranged structure but once incorporated in the ring, they are most frequently rearranged; i.e.
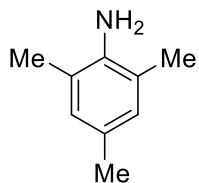

prim. alkyl halide
- unrearranged

(as hydrohalide salt)
n-propyl rearranged
to isopropyl
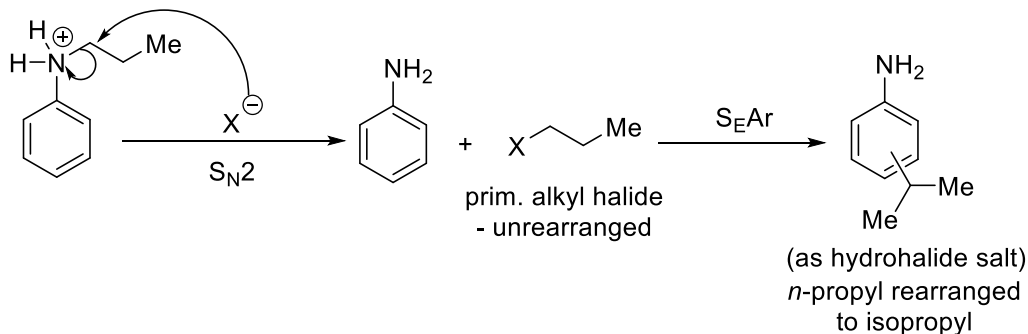
The rearrangement of the alkyl chain during S_EAr is reminiscent of the same as that seen in Friedel-Crafts alkylation.
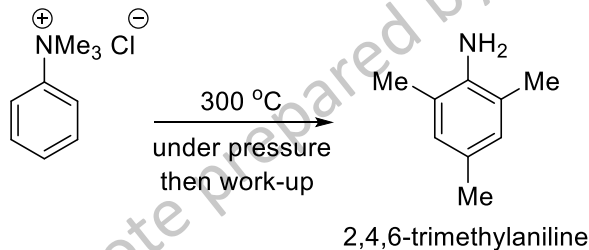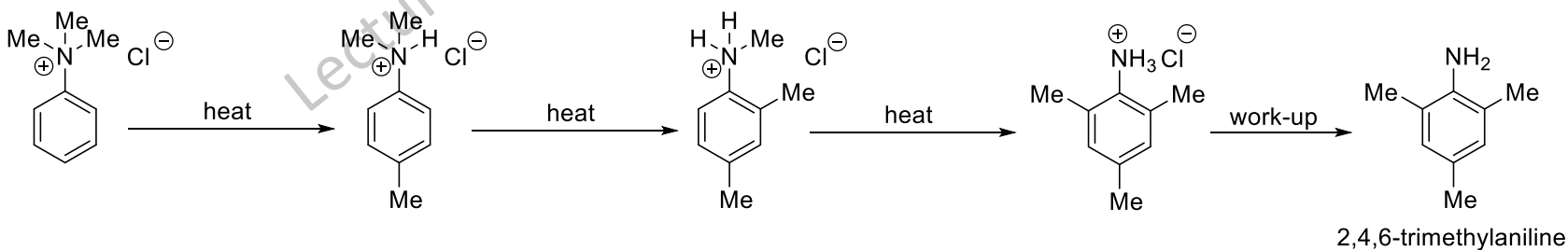
The rearranged carbocation is the electrophile in S_EAr

Synthetic utility:

Synthesis of

2,4,6-trimethylaniline

This is done by a series of Hofmann-Murtius rearrangements:

2,4,6-trimethylaniline

The reaction proceeds is a stepwise manner, one by one all three methyls migrate:
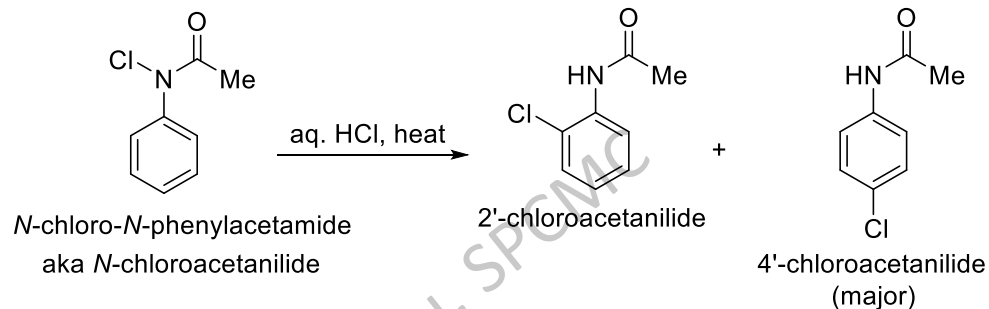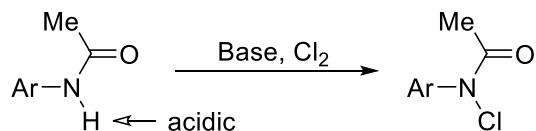

2,4,6-trimethylaniline

Rearrangements in Organic Chemistry

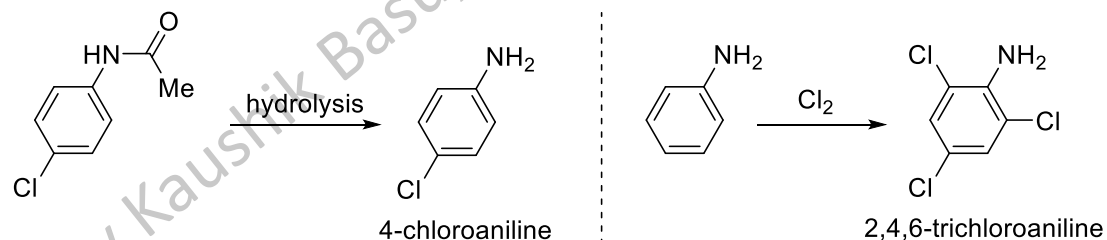Molecular rearrangement: Migration from side chain to aromatic rings: Orton rearrangement

Migration of halogen atom of *N*-haloanilides to the aromatic ring from the amide side chain on treatment with HX.
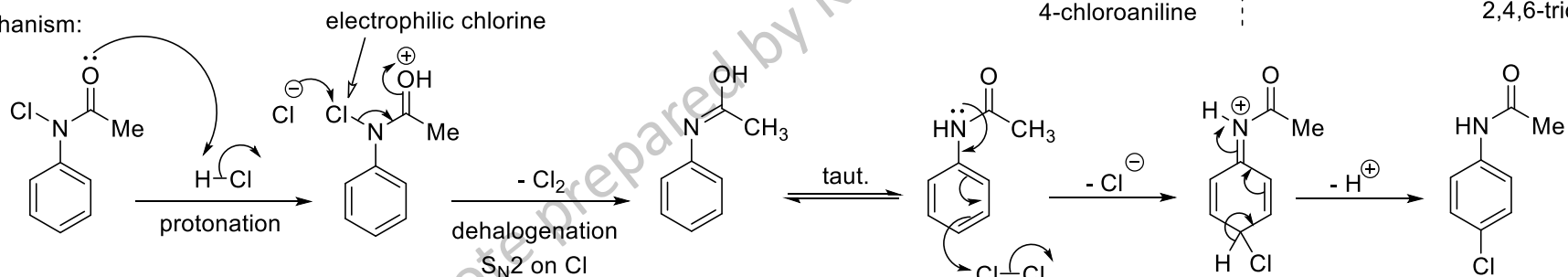
Synthesis of the *N*-haloanilide:

← acidic

Recall Hofmann degradation/rearrangement.

N-chloro-*N*-phenylacetamide
aka *N*-chloroacetanilide

aq. HCl, heat

2'-chloroacetanilide
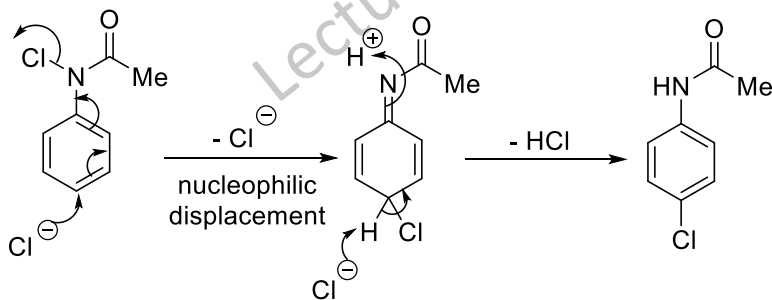
+

4'-chloroacetanilide
(major)

Synthtic utility of Orton rearrangement:

2'- or 4'-haloacetanilides are sources of 2- and 4-haloanilines, recall than monohalogenation of aniline is a challenge *via* SEAr

hydrolysis

4-chloroaniline

Cl_2

2,4,6-trichloroaniline

Mechanism:

electrophilic chlorine

$H-Cl$
protonation

$- Cl_2$
dehalogenation
S_N2 on Cl

taut.

$- Cl^{\ominus}$

$- H^{\oplus}$

Reaction of Cl_2 with acetanilide is a S_EAr
attack at *o*-position will lead to the minor product (sterics)

Alternative mechanistic proposal:

$- Cl^{\ominus}$
nucleophilic
displacement

$- HCl$

Rearrangements in Organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: Orton rearrangement
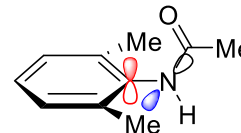
Proof :

1. Molecular chlorine has been recovered from reaction medium, thereby proving its *in situ* generation, and intermolecular nature of the reaction.

2. In presence of halogen captors, cross-halogenation take place - again proving that that halide is detached from the *N*-haloanilide, i.e. reaction is intermolecular.
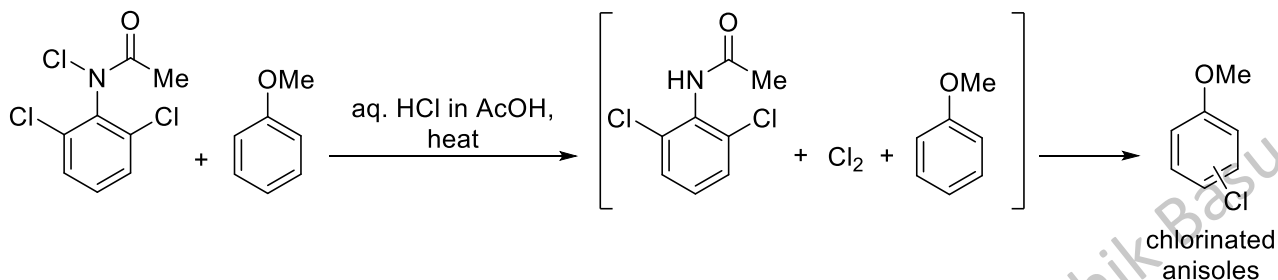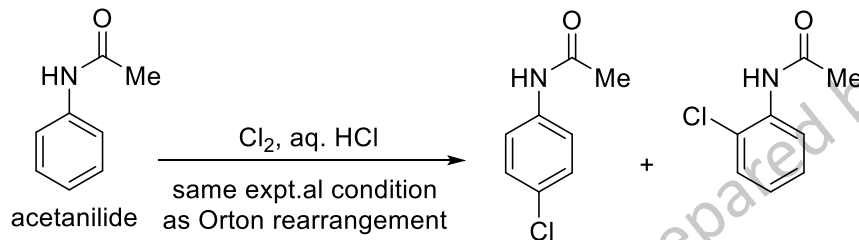

Anisole is more reactive than 2',6'-dichloroacetanilide towards SEAr.

The acetamido group in the anilide is forced out of the ring plane due to steric crowding with the two *ortho*-chlorines and thus, it cannot stabilize the σ-complex by conjugation.

This results in selective chlorination of anisole.

3. Chlorination experiment with acetanilide under Orton rearrangement reaction condition:

The *o-/p-* ratio of this reaction is exactly the same obtained from Orton rearranegement of *N*-chloroacetanilide. This concurs with the mechanism proposed where this SEAr is the endgame.

Effect of presence of other halides: When done in the presence of other HX acids (X = Br, I), Orton rearrangement of *N*-chloroacetanilides under hydrochloric acid afford the corresponding bromo- or iodo-derivatives.

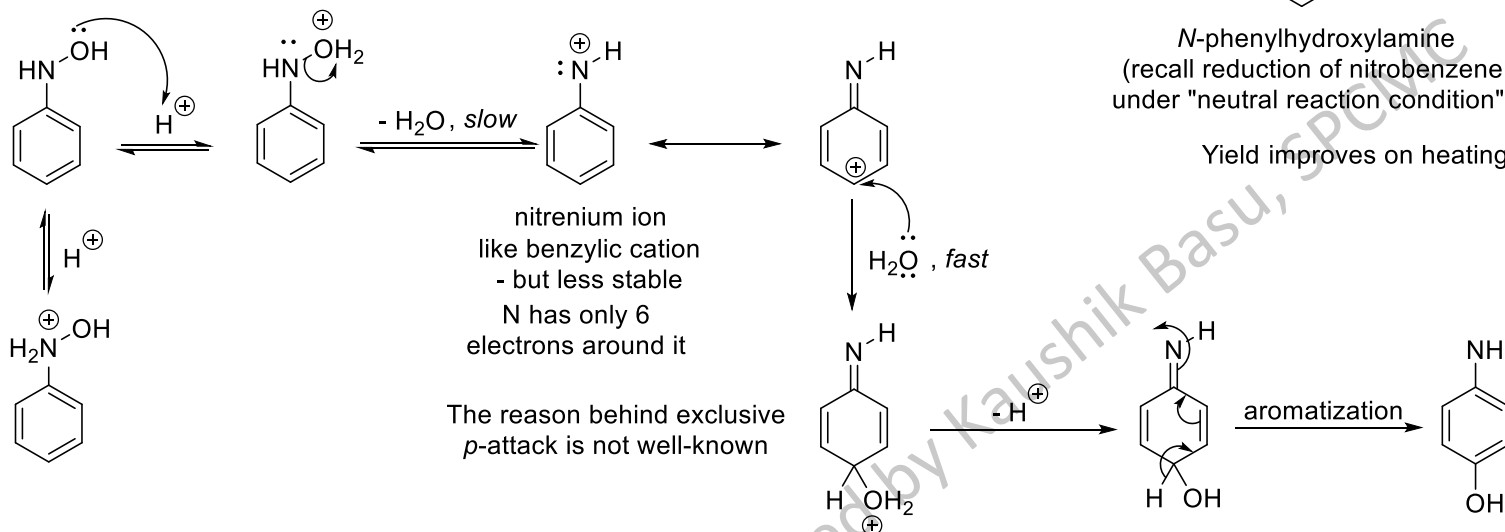both bromide and chloride are good nucleophiles

(o- + p-isomers)
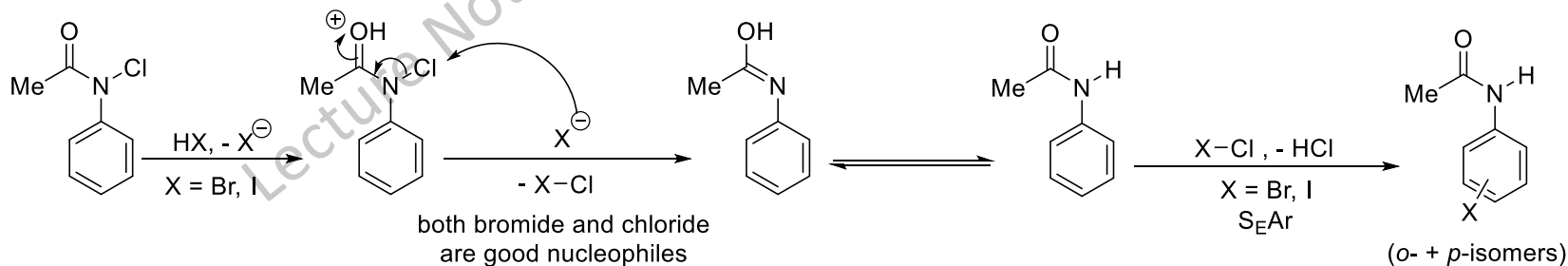
$\chi_{Cl} > \chi_{Br}, \chi_I$ X−Cl   X is the electrophilic end of X-Cl when X = Br, I, while the Cl⁻ is the LG, so X is introduced at the ring through S_EAr

Rearrangements in Organic Chemistry

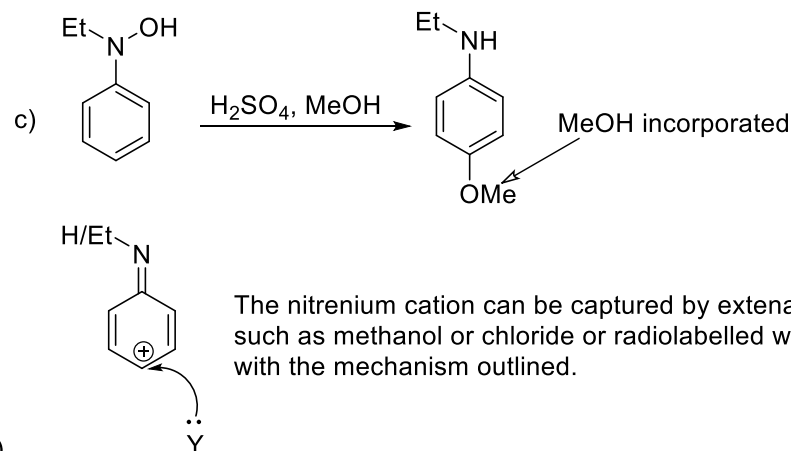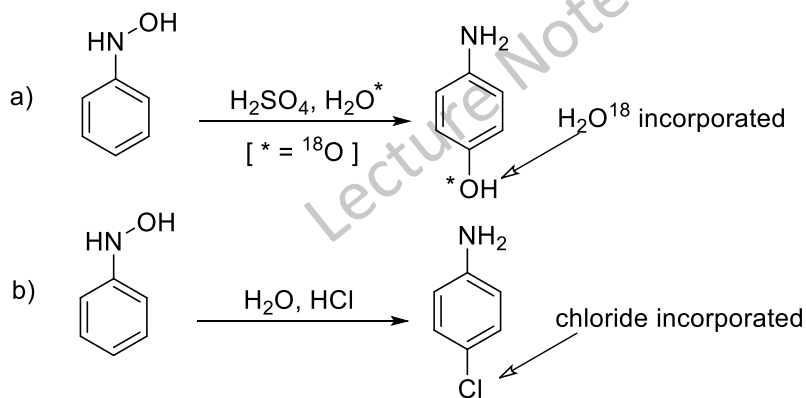Molecular rearrangement: Migration from side chain to aromatic rings: Bamberger rearrangement

Rearrangement of *N*-phenylhydroxylamine to 4-aminophenol under aq. acidic condition.
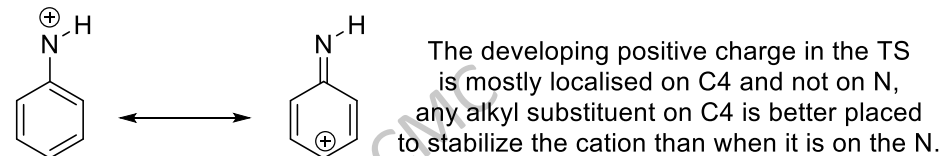
Mechanism:

N-phenylhydroxylamine
(recall reduction of nitrobenzene
under "neutral reaction condition")

4-aminophenol

Yield improves on heating the reaction mixture.

nitrenium ion
like benzylic cation
- but less stable
N has only 6
electrons around it

The reason behind exclusive
p-attack is not well-known
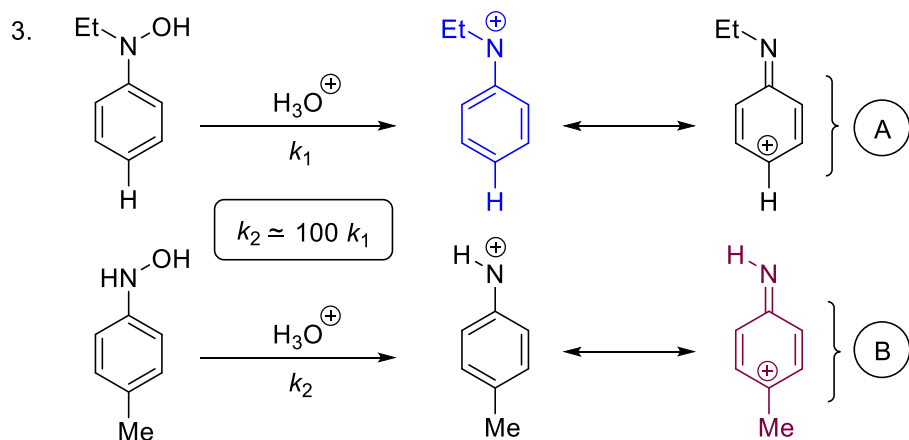
H_2O , *fast*

aromatization

Proof:

1. Kinetic studies reveal that the mechanism is S_N1 and not S_N2 as the rate is independent of the concentration of added nucleophiles.

2. The rearrangement is intermolecular in nature as proved by following experiments:
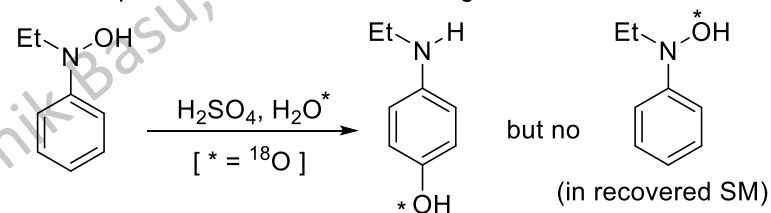
a) H_2SO_4, H_2O^* [* = ^{18}O]
H_2O^{18} incorporated

b) H_2O, HCl
chloride incorporated

c) $H_2SO_4, MeOH$
MeOH incorporated

The nitrenium cation can be captured by external nucleophiles (Y:) such as methanol or chloride or radiolabelled water. Concurrent with the mechanism outlined.

Rearrangements in Organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: Bamberger rearrangement
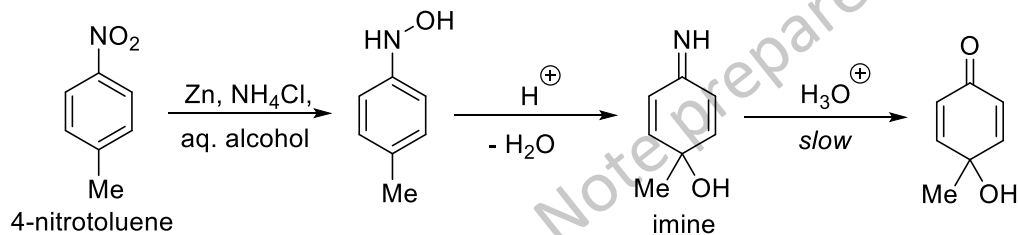
Proof (contd.):

3.

The developing positive charge in the TS is mostly localised on C4 and not on N, any alkyl substituent on C4 is better placed to stabilize the cation than when it is on the N.

$k_2 \simeq 100\, k_1$

Yet another proof of localization of + charge at C4:

$\xrightarrow[\text{[* = }^{18}\text{O]}]{\text{H}_2\text{SO}_4,\ \text{H}_2\text{O}^*}$

but no (in recovered SM)

B is more stable than A , forms faster, the corresponding SM reacts faster

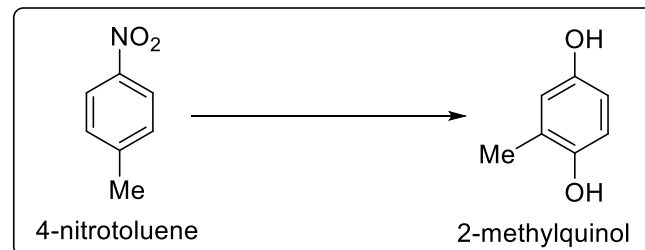Thus, we are forced to say that C4 carries bulk of the charge - nucleophile attacks that position.

The product from the 4-methyl derivative:

4-nitrotoluene

$\xrightarrow[\text{aq. alcohol}]{\text{Zn, NH}_4\text{Cl,}}$

$\xrightarrow[\text{- H}_2\text{O}]{\text{H}^\oplus}$

imine

$\xrightarrow[\text{slow}]{\text{H}_3\text{O}^\oplus}$

the substrate for dienone-phenol rearrangement that leads to 2-methylquinol.
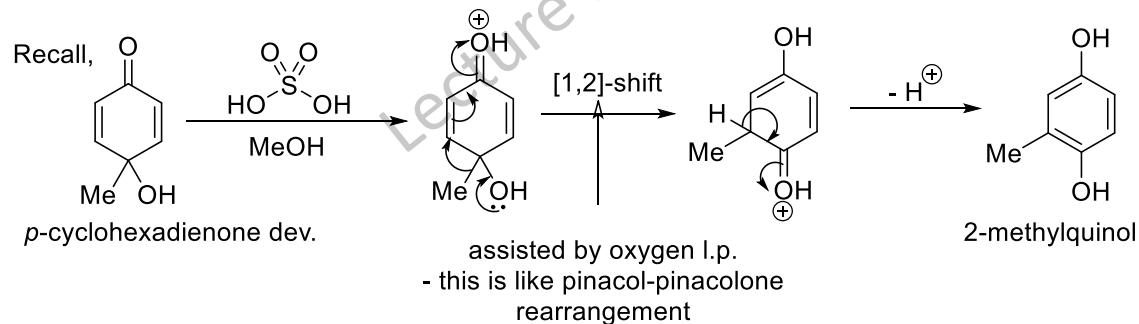
Therefore, combining the two rearrangements, Bamberger, followed by a dienone-phenol rearrangement, we can carry out the following conversion:

Recall,

p-cyclohexadienone dev.

$\xrightarrow[\text{MeOH}]{\text{HO-S(O)(O)-OH}}$

[1,2]-shift

$-\,\text{H}^\oplus$

2-methylquinol

assisted by oxygen l.p.
- this is like pinacol-pinacolone rearrangement

NO₂ / Me (4-nitrotoluene) → OH / Me / OH (2-methylquinol)

4-nitrotoluene   2-methylquinol

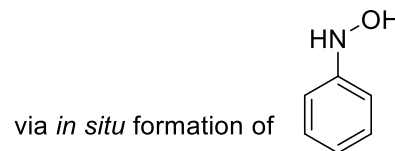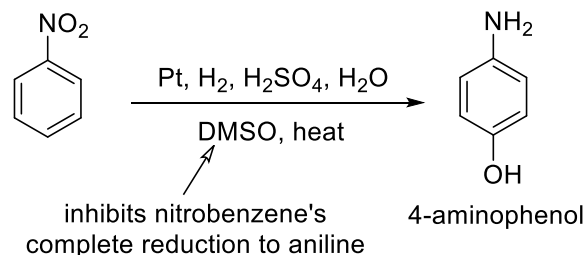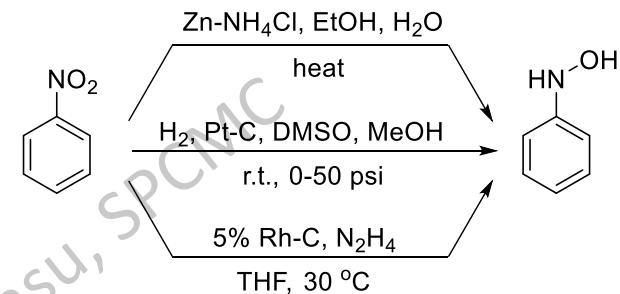# Rearrangements in Organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: Bamberger rearrangement
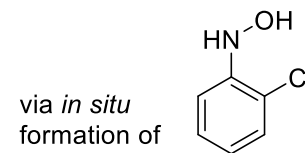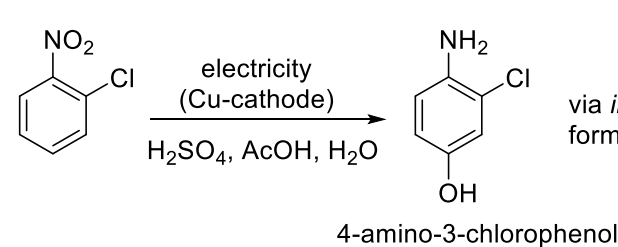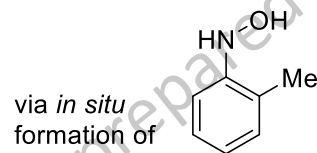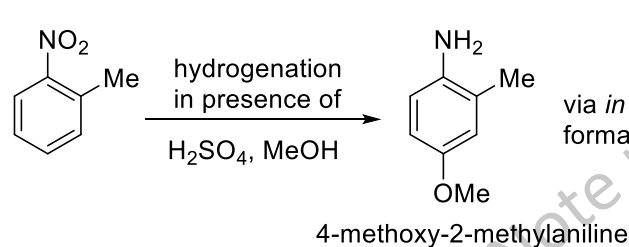
Synthetic utility:

Synthesis of arylhydroxylamine from nitroaromatics and subsequent functionalisation of the ring. Conventional method for hydoxylmamine synthesis is reducing the nitro compound with Zn-NH$_4$Cl, in aq. ethanol. But many other methods have been explored:

Nitroaromatic can directly be converted to the aminophenol or its dev. by modifying the reaction conditions so that reduction to hydroxyamine and Bamberger rearrangement proceed consecutively:
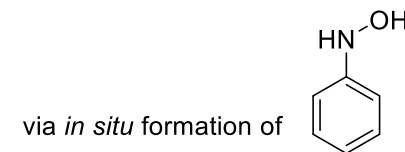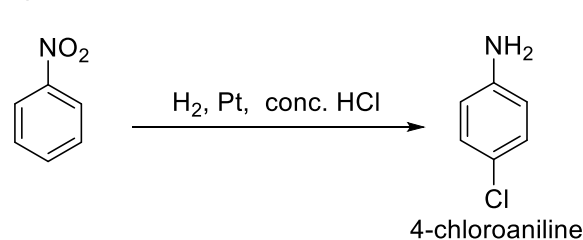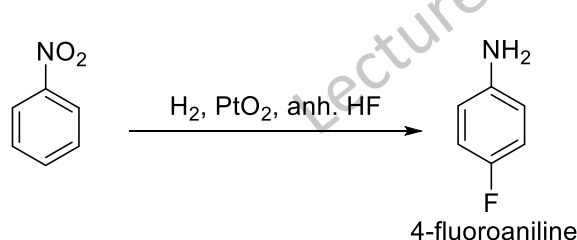
Methods to prepare *N*-phenylhydroxylamine from nitrobenzene:

inhibits nitrobenzene's complete reduction to aniline

4-aminophenol

via *in situ* formation of

Similarly,

4-methoxy-2-methylaniline

via *in situ* formation of

4-amino-3-chlorophenol

via *in situ* formation of

A good source of 4-haloanilines is the redution of nitrobenzene in presence of HX:

4-fluoroaniline

4-chloroaniline

via *in situ* formation of

Clearly, the halide nucleophile captures the nitrenium int. (at C4) that is formed during Bamberger rearrangement.
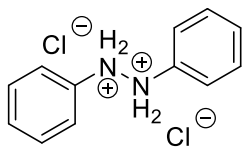
Rearrangements in Organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: Benzidine rearrangement (aka Zinin benzidine rearrangement):

Acid-catalysed conversions of hydrazoarenes into diaminobiaryls and amino diarylamines. These rearrangements are usually carried out in aqueous or ethanolic solutions of HCl or H_2SO_4.

1,2-diphenylhydrazine
(obtained by reduction of nitrobenzene under alkaline conditrion)

benzidine (almost 70%)

diphenyline (almost 30%)

o-benzidine

o-semidine

p-semidine

Observations:

1. Rate of the reaction = k [PhNHNHPh] $[H^+]^2$ First order w.r.t. 1,2-diphenylhydrazine, second order w.r.t. acid

   However, as the reactivity of the hydrazobenzene increases, rate dependence on acid concentration decreases.

2. With where * = ^{15}N, we have PKIE, meaning that the N-N bond breaks in RDS

   but with we have no PKIE meaning that the C-D bond *does not* break in RDS

3. there are no cross products in crossover experiments, meaning intramolecular nature of the reaction:

Rearrangements in Organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: Benzidine rearrangement (aka Zinin benzidine rearrangement):
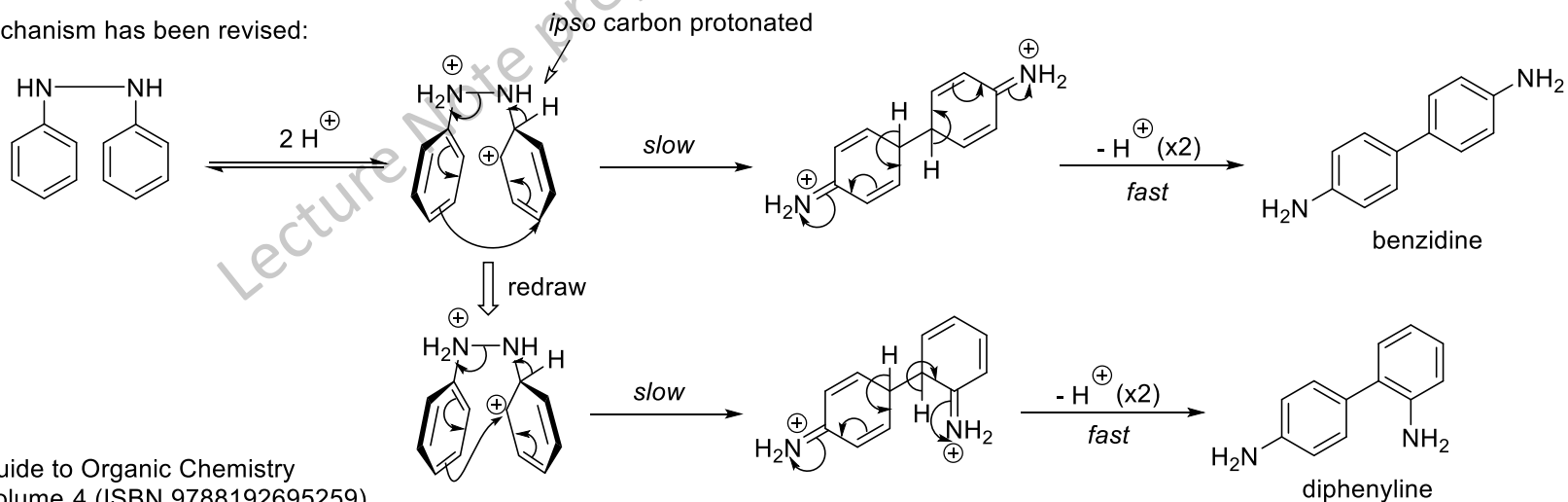
Mechanism:
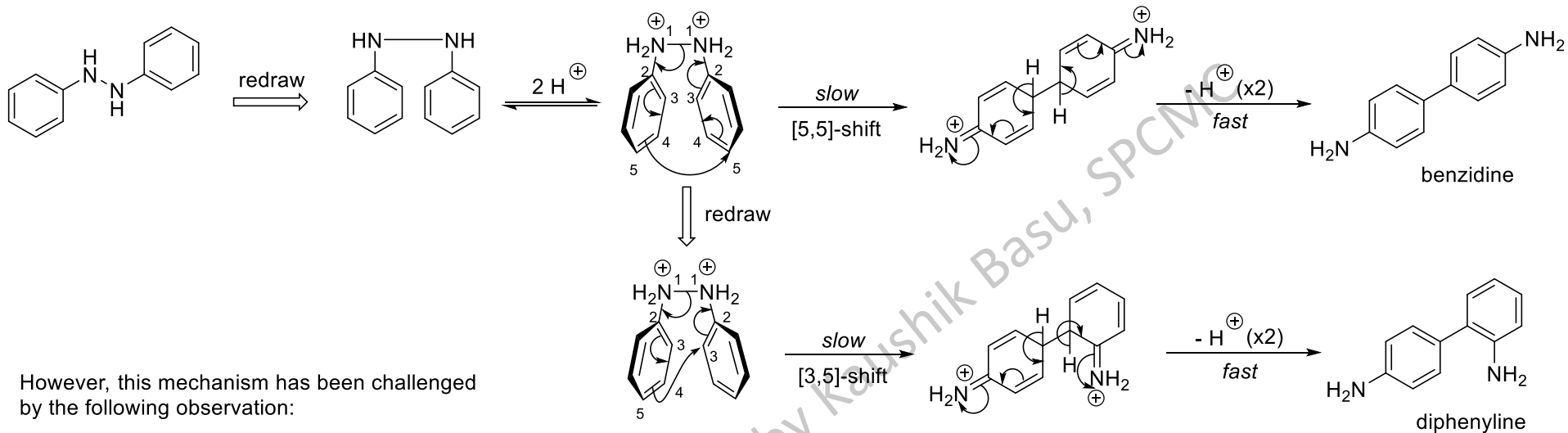
However, this mechanism has been challenged by the following observation:

prepared independently, *does not* undergo benzidine rearrangement when subjected to the reaction condition.

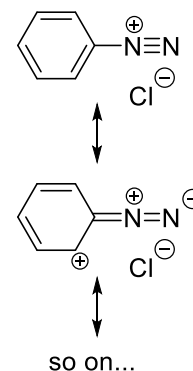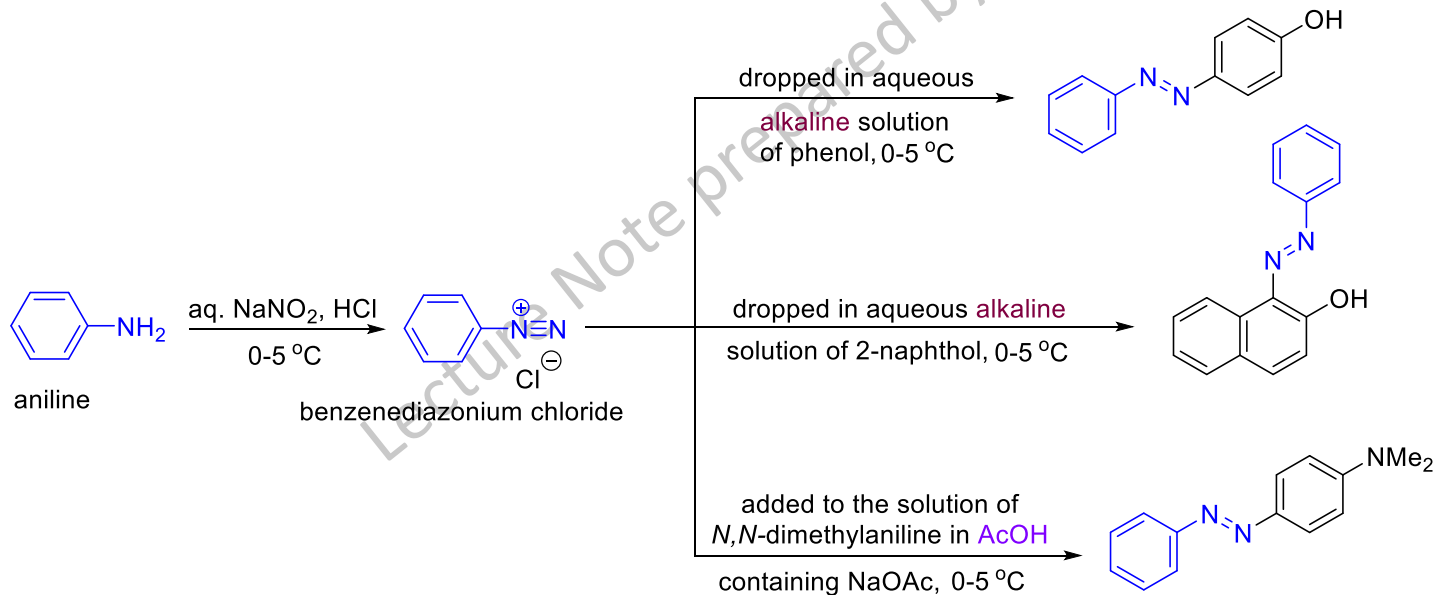So the mechanism has been revised:

Rearrangements in Organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: *N*-azo to *C*-azo rearrangement:

Diazotization of aniline affords the benzenediazonium salt:

nitrosonium ion, resonance-stabilized
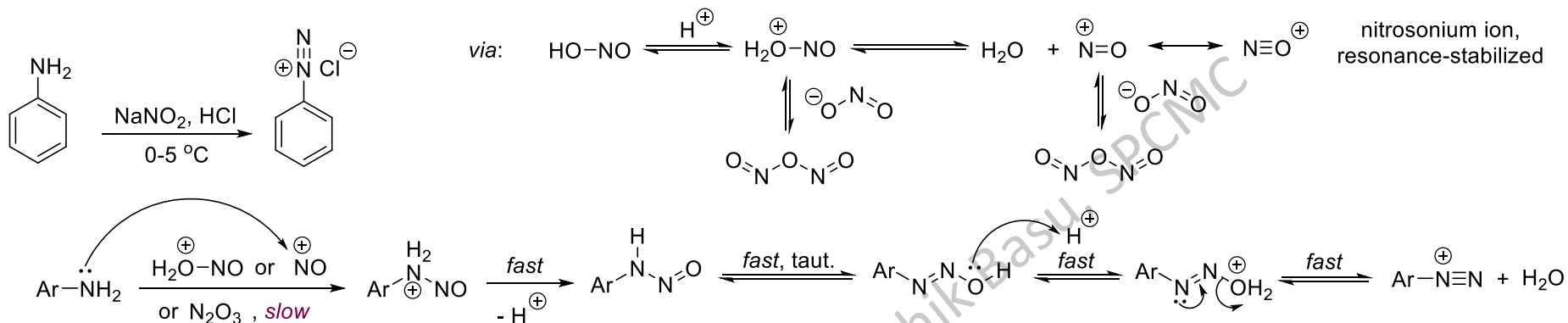
N-nitrosation is driven by kinetic control

The diazonium salts undergo diazo coupling (azo coupling) reactions when reacted with aromatic substrates carrying rings activated towards S_EAr:
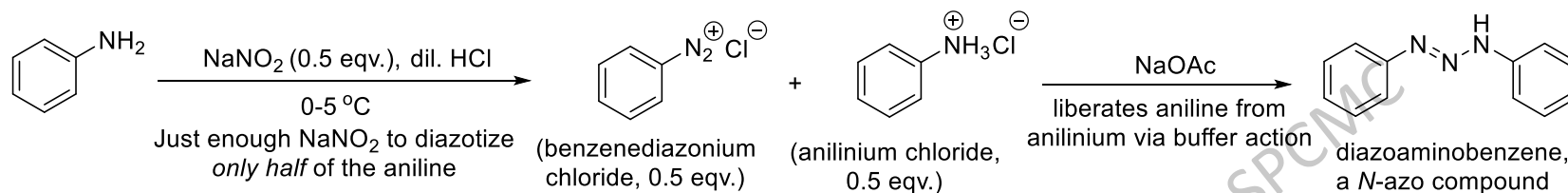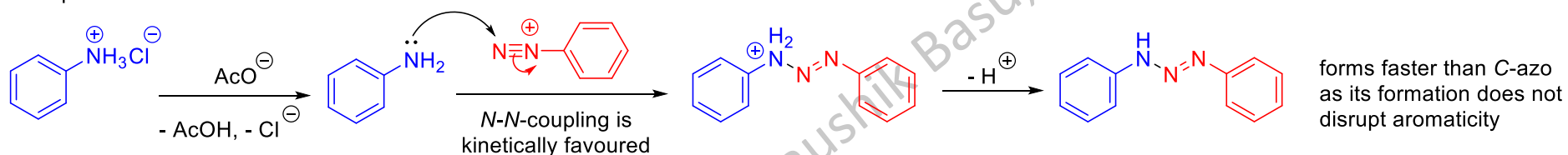

aniline

aq. NaNO$_2$, HCl
0-5 °C

benzenediazonium chloride

dropped in aqueous alkaline solution of phenol, 0-5 °C

dropped in aqueous alkaline solution of 2-naphthol, 0-5 °C

added to the solution of *N,N*-dimethylaniline in AcOH containing NaOAc, 0-5 °C

benzenediazonium ion is rsonance-stabilized; hence it is a weak electrophile and couple only with highly activated rings.

so on...

Rearrangements in Organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: *N*-azo to *C*-azo rearrangement:

The benzenediazonium salt can couple with primary aromatic amines as well. In that case a *N-N* coupling is seen:

(benzenediazonium chloride, 0.5 eqv.)

(anilinium chloride, 0.5 eqv.)

diazoaminobenzene, a *N*-azo compound

NaNO$_2$ (0.5 eqv.), dil. HCl, 0-5 °C

Just enough NaNO$_2$ to diazotize *only half* of the aniline

NaOAc liberates aniline from anilinium via buffer action

Reaction proceeds via:

AcO$^{\ominus}$, - AcOH, - Cl$^{\ominus}$

N-N-coupling is kinetically favoured

- H$^{\oplus}$

forms faster than *C*-azo as its formation does not disrupt aromaticity

This *N*-azo compound, on heating with acid gets converted to the corresponding *C*-azo compound:

diazoaminobenzene, a *N*-azo compound

warmed with aq. HCl

aminoazobenzene, a *C*-azo compound
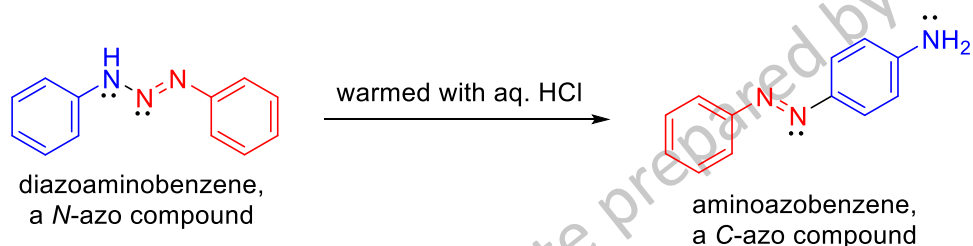
The *C*-azo is more stable than the *N*-azo, as it is conjugated and free of weaker N-N bond (l.p.-l.p.repulsions).

This is a rearrangement where the migrating group (Ph-N=N) migrates from N to the ring - just like the series of rearrangements we've seen.

This conversion is akin to transfroming the KCP into the TCP.

If the *p*-position of the anilino group is already occupied then the rearrangement is slower and the migrating group ends up at the *o*-position.
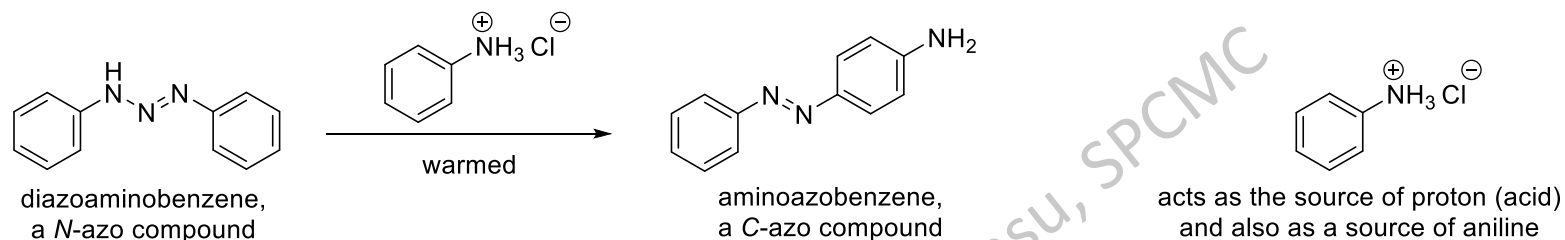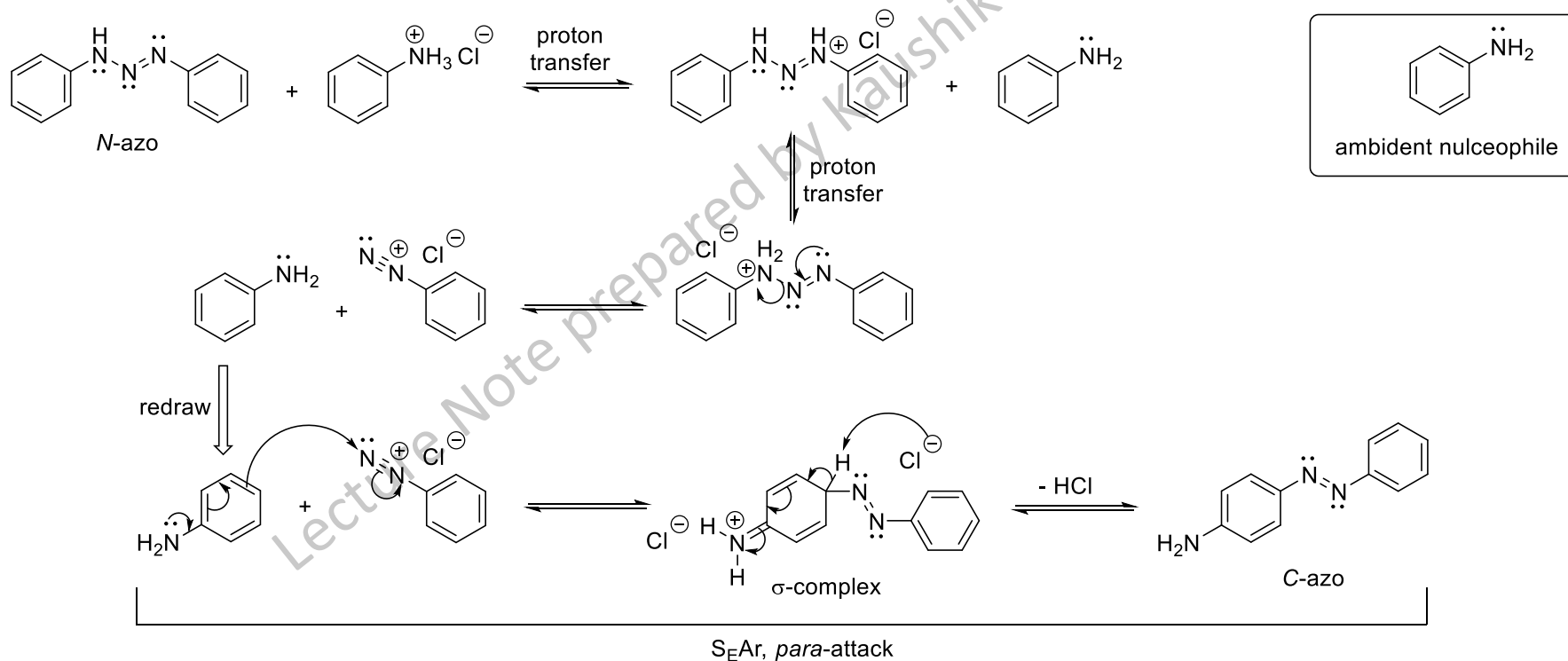
Note on nomenclature:
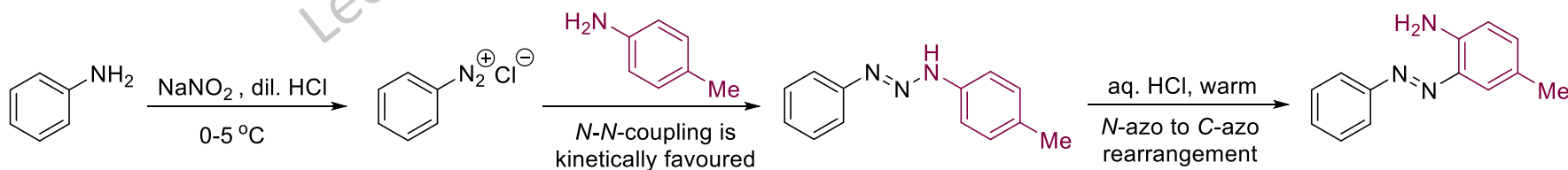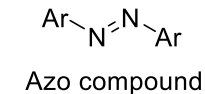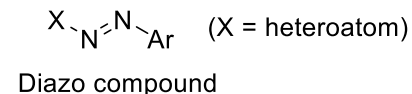
X$\diagdown$N$\diagup$N$\diagdown$Ar   (X = heteroatom)

Diazo compound

Ar$\diagdown$N$\diagup$N$\diagdown$Ar

Azo compound

NaNO$_2$, dil. HCl, 0-5 °C

N-N-coupling is kinetically favoured

aq. HCl, warm *N*-azo to *C*-azo rearrangement

Rearrangements in Organic Chemistry

Molecular rearrangement: Migration from side chain to aromatic rings: *N*-azo to *C*-azo rearrangement:

The diazoaminobenzene to aminoazobenzene convesrion can also be carried out, and more efficiently, by heating the *N*-azo compound with aninilium chloride (aka aniline hydrochloride, the salt derived from aniline and hydrogen chloride).
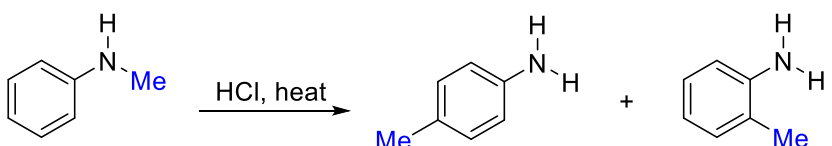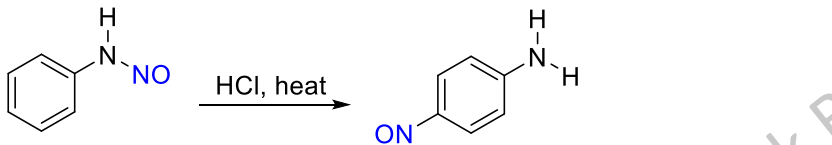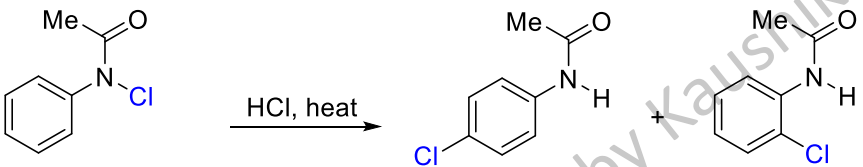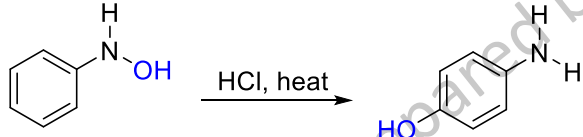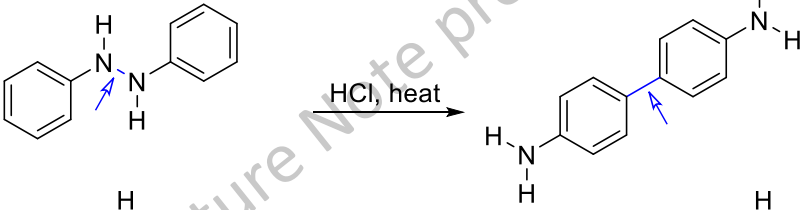

diazoaminobenzene,
a *N*-azo compound

aminoazobenzene,
a *C*-azo compound

acts as the source of proton (acid)
and also as a source of aniline

Mechanism:

N-azo

proton transfer

proton transfer

ambident nulceophile
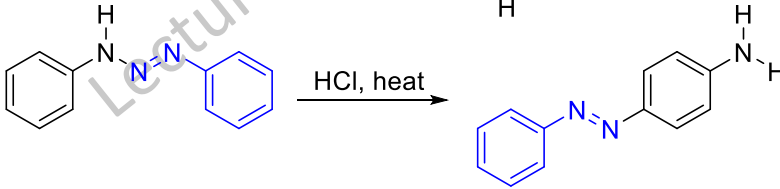
redraw

σ-complex

- HCl
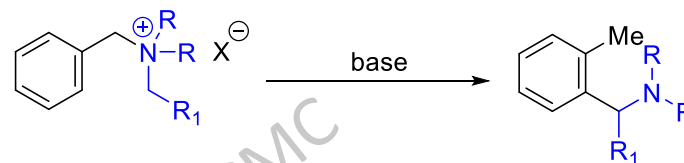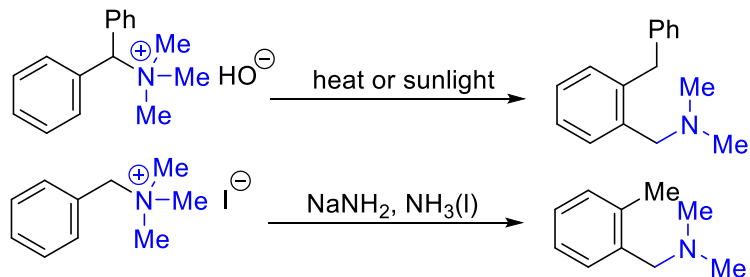
C-azo

S$_E$Ar, *para*-attack

Rearrangements in Organic Chemistry

Molecular rearrangement: Migration from N-atom of side chain to aromatic rings: A summary -

Name	Reaction	Migrating group
Hofmann-Martius		Alkyl groups like methyl
Fischer-Hepp		nitroso (NO)
Orton		chlorine
Bamberger		hydroxyl
Zinin Benzidine		N-N σ-bond
Diazoamino to aminoazo rearrangement		phenyldiazo

A. W. Hofmann
(1818-1892)

C. A. von Murtius
(1838-1920)

O. P. Fischer
(1852-1932)

K. J. P. Orton
(1872-1930)

E. T. Bamberger
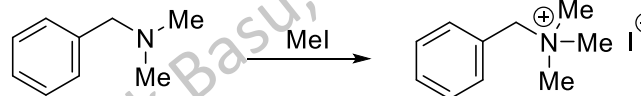(1857-1932)

N. N. Zinin
(1812-1880)

Rearrangements in Organic Chemistry

Molecular rearrangement: Migration from N-atom of side chain to aromatic rings: Sommelet-Hauser rearramgement
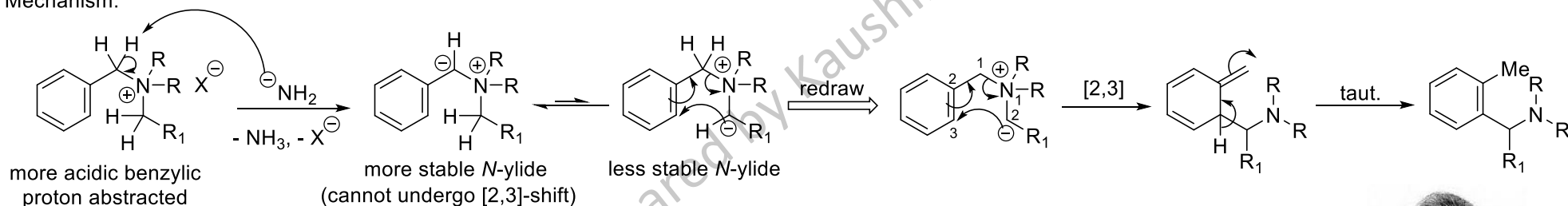
A base-mediated aromatic [2,3] sigmatropic rearrangement of a nitrogen ylide generated
from a quaternary ammonium salt possessing a benzyl substituent :

Synthesis of quaternary ammonium salt:
by alkylating the corresponding teriary amines:

Mechanism:

more acidic benzylic
proton abstracted

more stable *N*-ylide
(cannot undergo [2,3]-shift)

less stable *N*-ylide

Important limitations:

1. S-H rearrangement can take place on substrates containing a substituted benzene ring, but if the initial benzylic carbanion is
significantly stabilized due to the presence of any EWG (e.g. CN, NO$_2$, Cl, Br) on the ring, then the ylide required for [2.3]-shift may
not form at all, and the reaction may not occur then.

C. R. Hauser
(1900-1970)

abstraction would lead
to an alkene
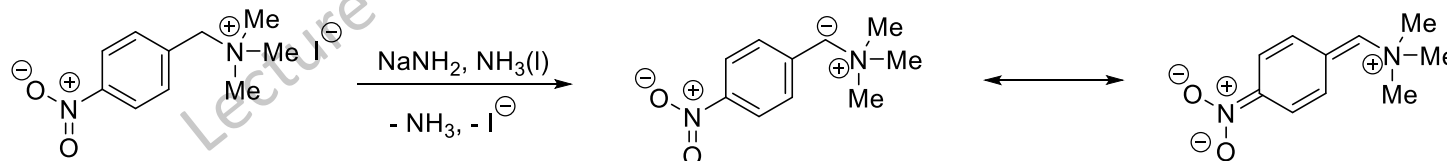
2. When the alkyl groups attached to the nitrogen contain a hydrogen atom at their β-position,
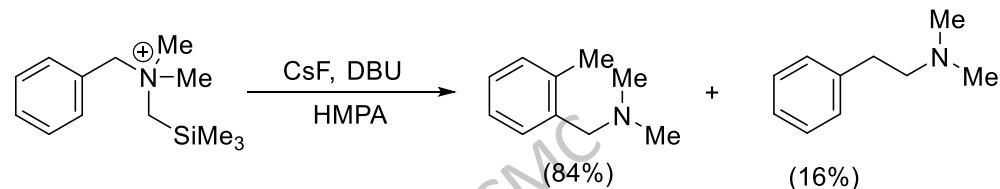the Hofmann elimination may compete
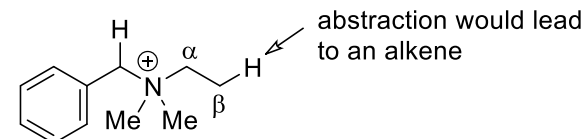
Rearrangements in Organic Chemistry

Molecular rearrangement: Migration from N-atom of side chain to aromatic rings: Sommelet-Hauser rearramgement

Important limitations (contd.):

3. Depending on the substrate and reaction conditions,
the S-H rearrangement competes with the 1,2-Stevens rearrangement.

(84%) + (16%)

In the given example, the ylide is generated by fluoride-induced desilylation:

homolysis of
C(1)-N⁺(1) bond | 1,2-Stevens
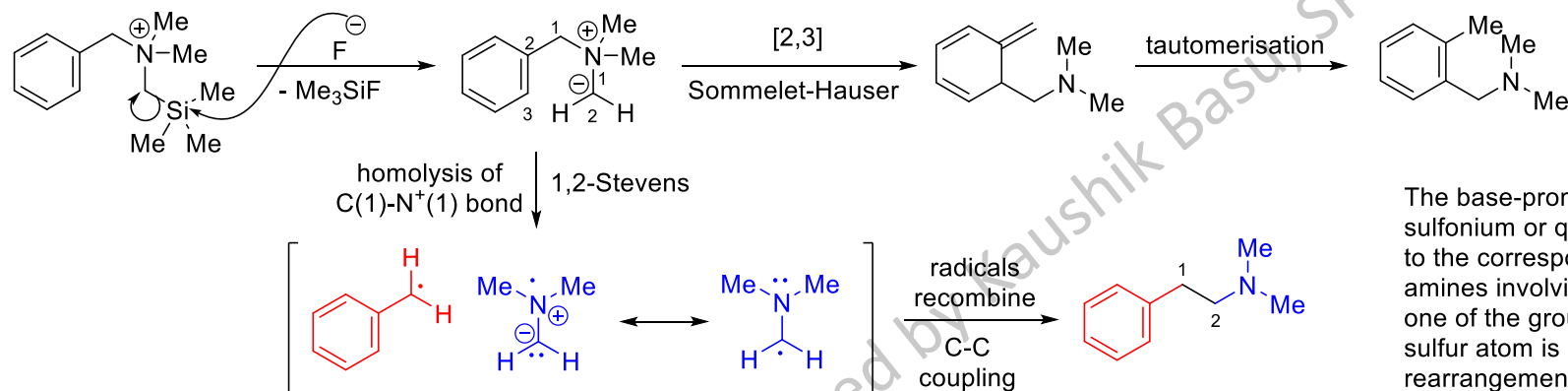
The base-promoted transformation of sulfonium or quaternary ammonium salts to the corresponding sulfides or tertiary amines involving the [1,2]-migration of one of the groups on the nitrogen or sulfur atom is known as the [1,2]-Stevens rearrangement.

In systems where both the Stevens- and S-H rearrangements are possible, the choice of reaction conditions allow control over which of these competing processes dominate; low temperatures and polar solvents (e.g., NH_3, DMSO, HMPA) usually favor the S-H rearrangement, whereas higher temperatures and nonpolar solvents (e.g., hexanes, ether) facilitate the Stevens rearrangement;

Utility of S-H rearrangement:

1. At the expense of a C-N bond we get a C-C bond in this reaction, at the o-position w.r.t. the original benzylic substitutent. Used en route synthesis of complex organic targets (discussion beyond our scope).

2. Cyclic quaternary ammonium salts react by ring-expansion: