Organic Chemistry-4

Semester-4, CBCS

Course: CEMA CC-4-8-TH

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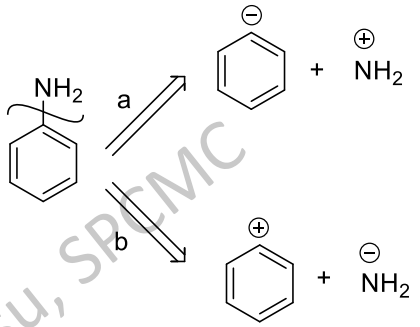
Recommended texts:

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

Synthesis of aromatic amines:

Formation of C-N bond is easier, therefore, we may consider the following disconnections in order to plan for a synthesis of an aromatic primary amine, such as aniline:



Disconnection 'a' will require an electrophilic substitution on the benzene ring with a particular electrophilic nitrogen fragment, which is difficult to get hold of.

Disconnection 'b' will require a nucleophilic substitution on a suitably substituted benzene ring (e.g. chlorobenzene) by amide ion. This is certainly doable (recall the benzyne mechanism) but definitely not a generalised technique.

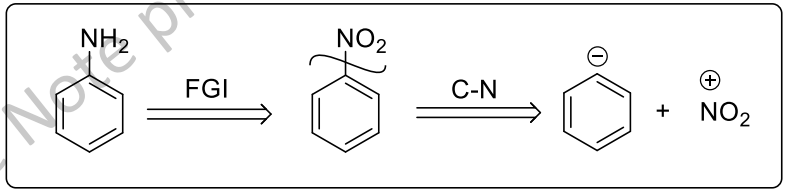
Way out?

We need to revise the target to something which can be converted, preferably easily, into an aromatic amine. That is to say that in terms of retrosynthesis, we need to do a functional group interconversion (FGI).

FGI: The operation of writing one functional group for another so that disconnection becomes possible. The reverse of a chemical reaction.

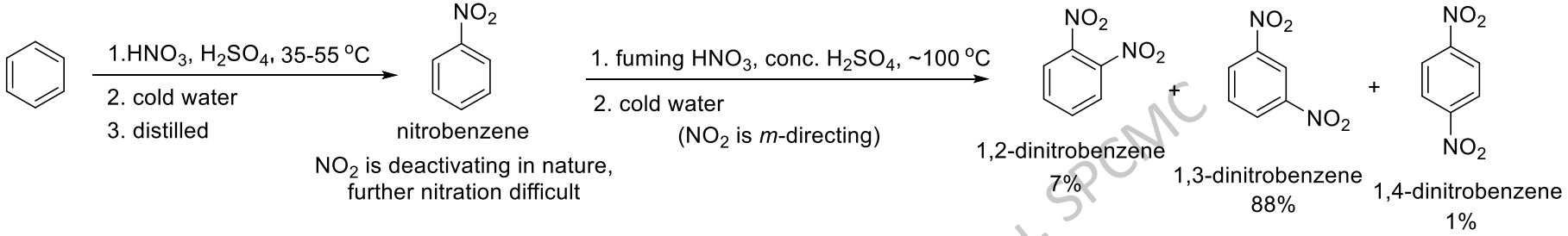
Recall that there are reliable reduction methods to convert aromatic nitro compounds to the corresponding amines, and there are also a number of techniques for introducing a nitro group onto a benzene ring.

Thus, nitration of aromatic rings and subsequent reduction of the resultant nitro compounds is a standard protocol for synthesis of aromatic primary amines.

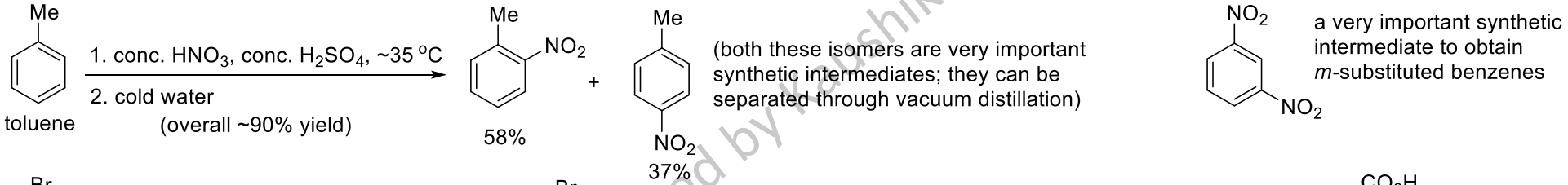


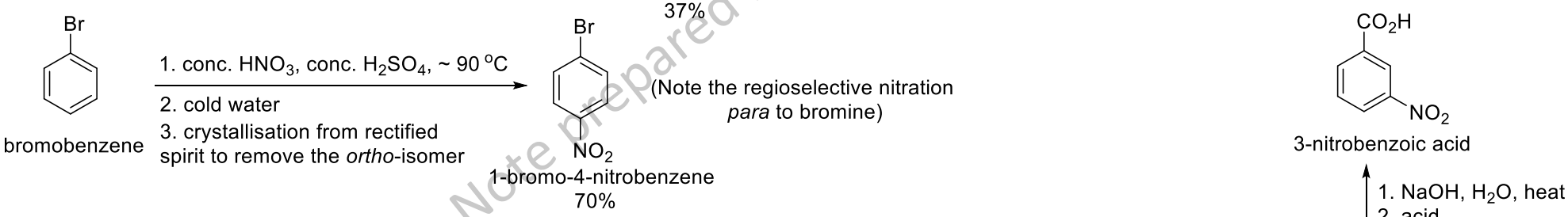
In semester III, we have learned (hopefully!) the lot about nitration reaction, the reagents, substrates, reaction condition and associated selectivity. The following slides presents a summary of these. However, our focus this time is on the reduction methods of the nitroarenes into the corresponding amino derivatives.

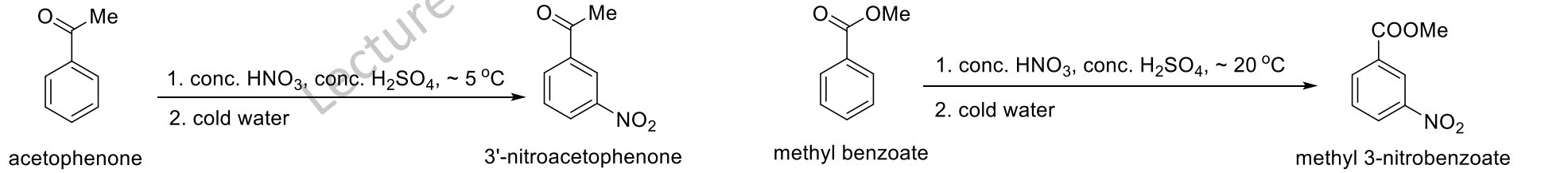
Nitration: Electrophile is nitronium ion, commonly generated from the nitrating mixture i.e. conc. HNO_3 and conc. H_2SO_4 mixture. $O{=}\overset{\oplus}{N}{=}O$



The mixed acid reagent can also be used for the nitration of aromatic rings containing weakly activating or weakly deactivating substituents.

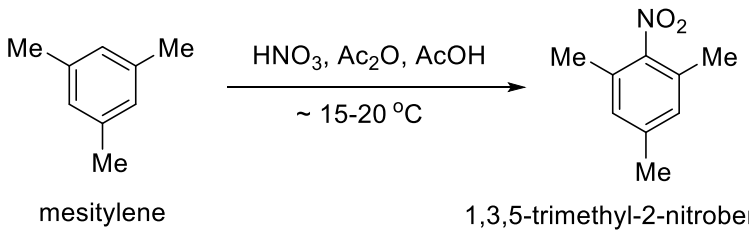






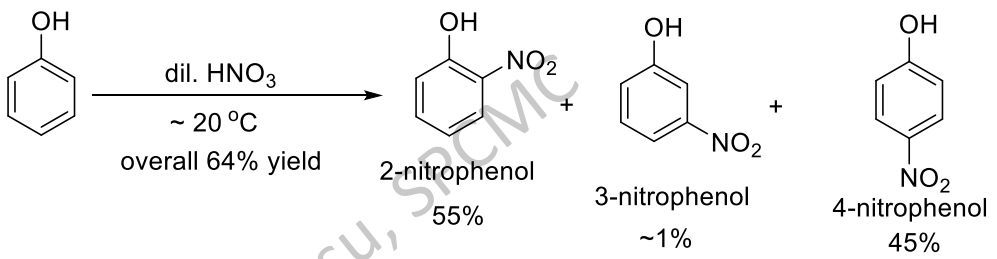
nitration of benzoic acid is difficult with nitrating mixture - solubility problem.

Nitration: The nitric acid-sulphuric acid mixture is too powerful a nitrating agent to be used with strongly activated aromatic nuclei. Nitric acid in water or in an organic solvent is often a milder alternative to effect mononitration of strongly activated aromatic rings.



mesitylene

1,3,5-trimethyl-2-nitrobenzene



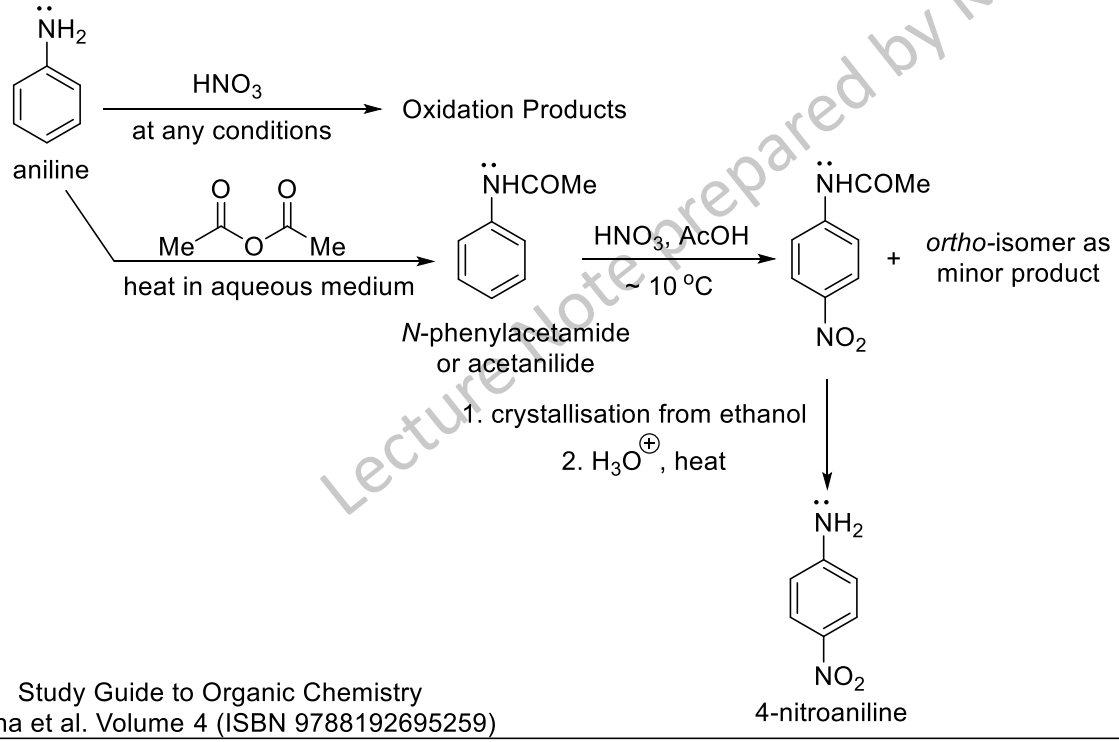
2-nitrophenol
55%

3-nitrophenol
~1%

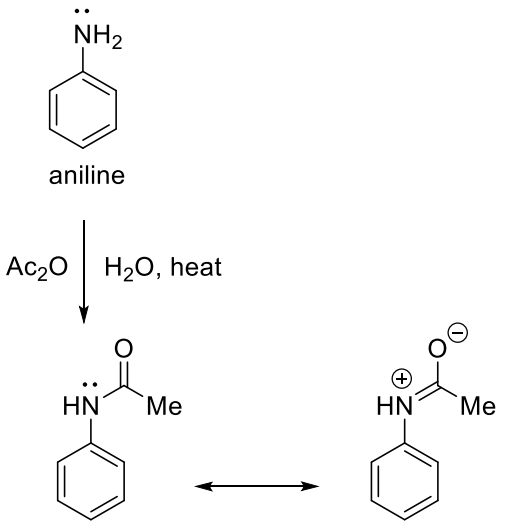
4-nitrophenol
45%

The *ortho*- and *para*-isomers can be separated by steam distillation. Because of the presence of intramolecular hydrogen bonding in the *ortho*-isomer, it has a lower boiling point and is therefore steam volatile.

Nitration of highly activated aromatic rings such as aromatic amines is difficult, as common nitration agents tend to oxidize the electron-rich aromatic nucleus instead of nitrating it. In such cases, the activating (electron-donating) influence of amino group must be reduced somewhat.



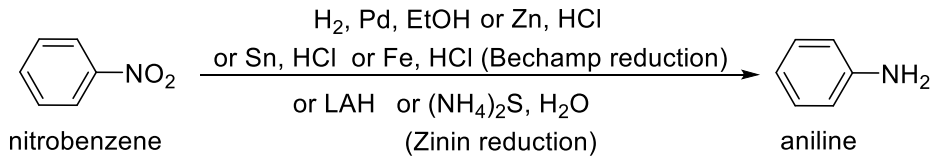
4-nitroaniline



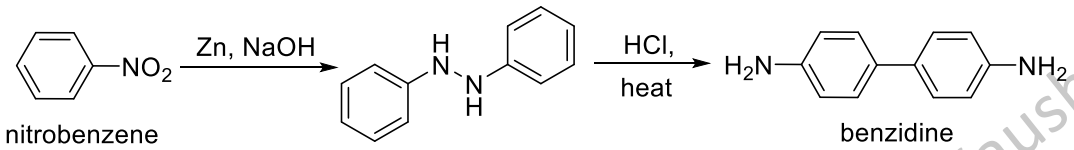
cross-conjugation, electron flow into the ring is controlled, acetanilide is less susceptible to oxidation than aniline.

Reducing the nitro group:

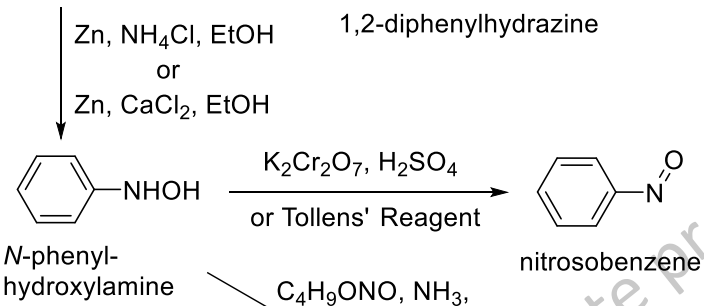
Reduction of nitro group affords different products under different conditions, which can be manipulated further.



nitrobenzene — aniline

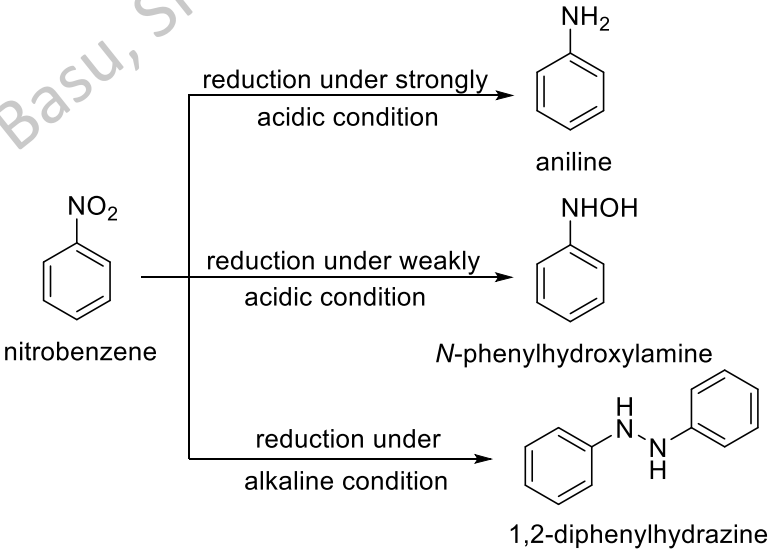


nitrobenzene — 1,2-diphenylhydrazine — benzidine — benzidine rearrangement



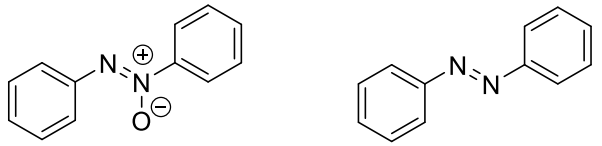
N-phenyl-hydroxylamine — nitrosobenzene — 4-aminophenol — cupferron, used to estimate Cu^{+2} and Fe^{+3}

The nature of the final reduction product of nitrobenzene depends on the pH of the medium:



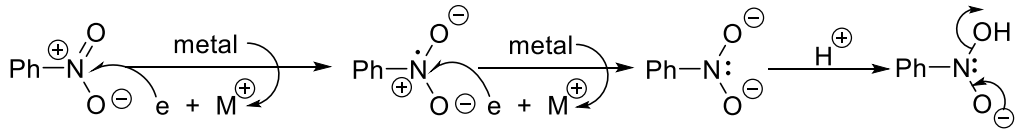
nitrobenzene

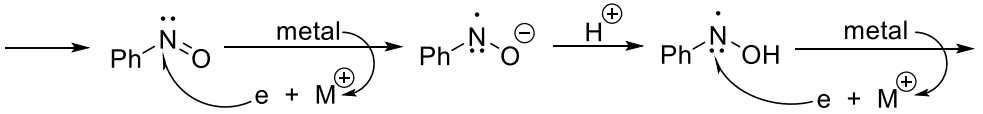
In addition to the above, the final product also depends on the nature of the reducing agent used. A few complex compounds that may also be obtained are: azoxybenzene, azobenzene etc.

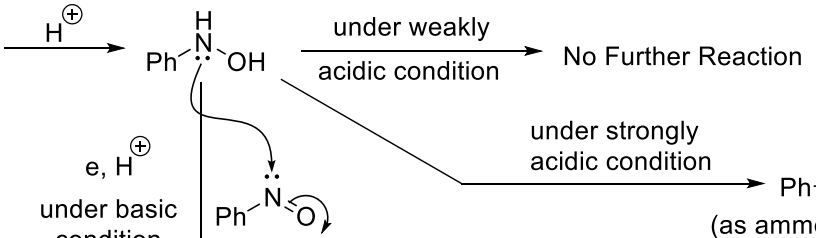


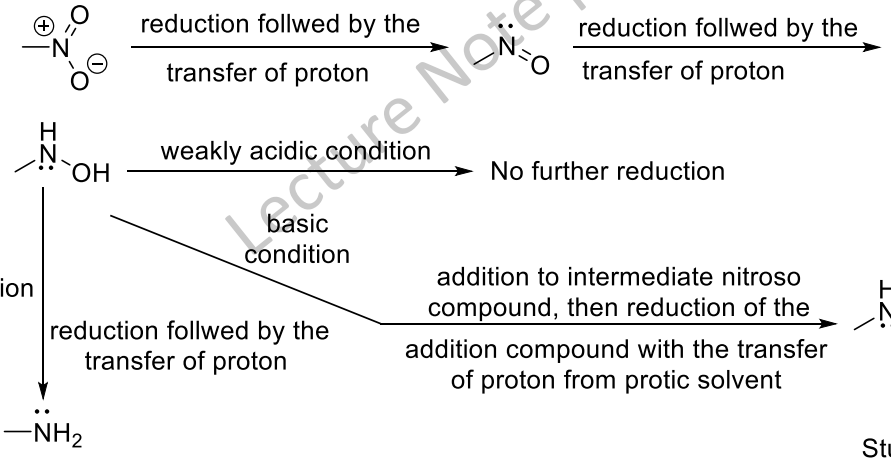
Organonitrogen Chemistry

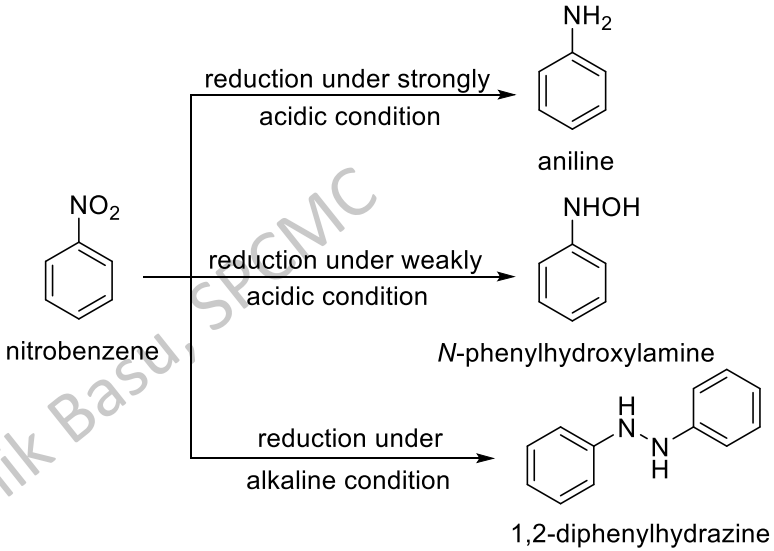
Reducing the nitro group: Mechanistic description:



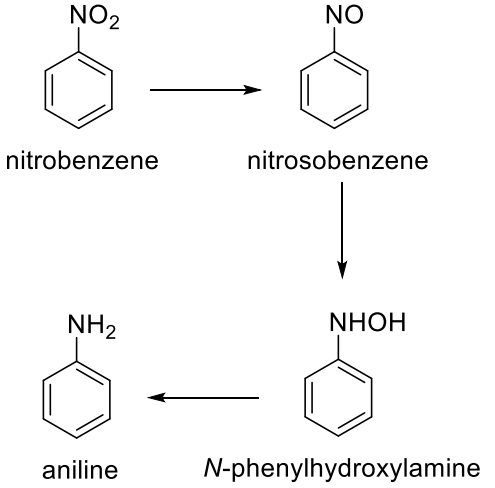






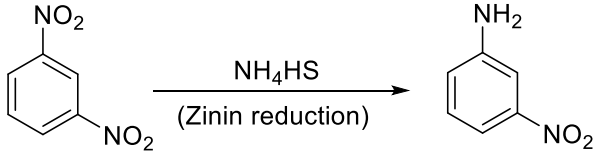


various intermediates *en route* of amino from nitro:



Organonitrogen Chemistry

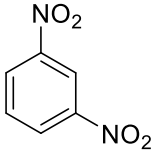
Regarding the reduction of aromatic nitro compounds it is very important to note a useful and selective reducing action exhibited by aqueous or aqueous alcoholic ammonium or alkali metal sulfides or polysulfides or hydrogen sulfides. These reagents smoothly reduce one nitro group in a polynitro compound to yield the corresponding nitroamine e.g. *m*-nitroaniline from *m*-dinitrobenzene:



1,3-dinitrobenzene — 3-nitroaniline

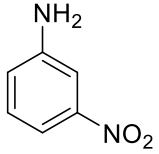
In order to understand why only one nitro group is reduced, we need to consider the following facts:

A]



1,3-dinitrobenzene

better oxidant, two EW NO_2 group



3-nitroaniline

weaker oxidant, one EW NO_2 group, one ER NH_2 group

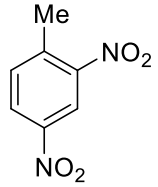
Reactant has more tendency to get reduced than the product, so a selective reduction is theoretically possible.

B] The reducing agent here is sulfide ion which is oxidized to sulfur. This sulfur can form a polysulfide with the reducing agent sulfide ion in the reaction medium. As a result, the negative charge over the sulfide ion is dispersed and which compromises the reducing ability of the reducing agent in the reaction medium, i.e., reduction power is decreased. As the reducing agent becomes less agressive with the progress of the reduction chances of executing a selective reduction is better.

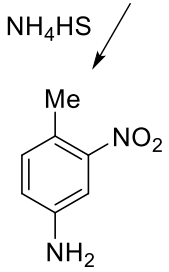
With the proper choice of reagent and reaction condition, it is possible to stop the reduction of polynitro compounds at a stage where only one of the nitro groups is reduced.

This is what happens here.

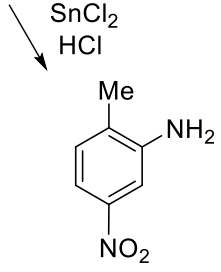
It is also evident why the polysulfides are more suitable for effecting such a selective reduction. Stannous chloride in hydrochloric acid is another reagent for selective reduction.



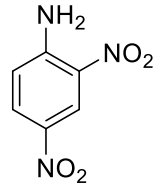
2,4-dinitrotoluene



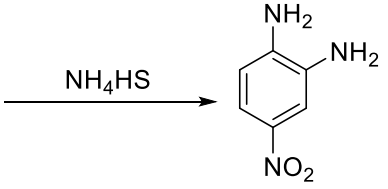
4-methyl-3-nitroaniline



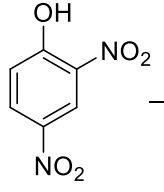
2-methyl-5-nitroaniline



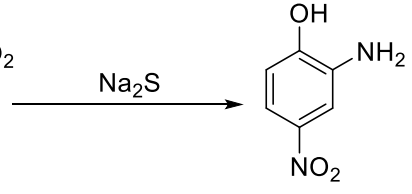
2,4-dinitroaniline



4-nitrobenzene-1,2-diamine



2,4-dinitrophenol

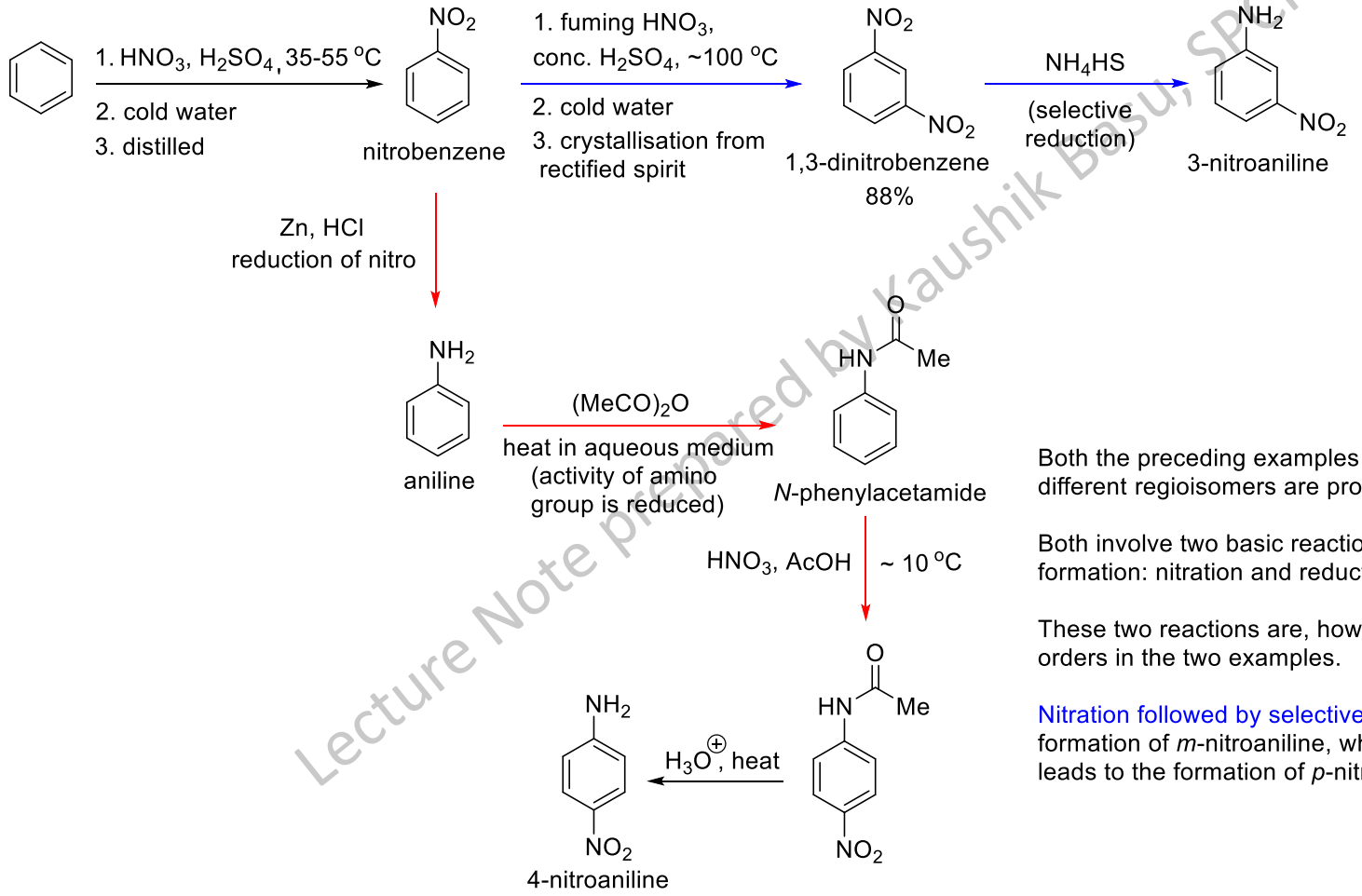


2-amino-4-nitrophenol

Exploiting the orientation effect of nitro group in S_EAr to solve regioselectivity issues:

Nitro group is *meta*-orienting but gets converted to amino group after reduction which is *ortho*-/*para*-orienting.

Thus a proper selection of the order of reactions, the reduction of nitro group and the electrophilic substitution, may lead to the formation of product with our desired orientation.



Both the preceding examples involve synthesis of nitroanilines but different regioisomers are produced in each.

Both involve two basic reactions after nitrobenzene formation: nitration and reduction of the nitro group.

These two reactions are, however, carried out in different orders in the two examples.

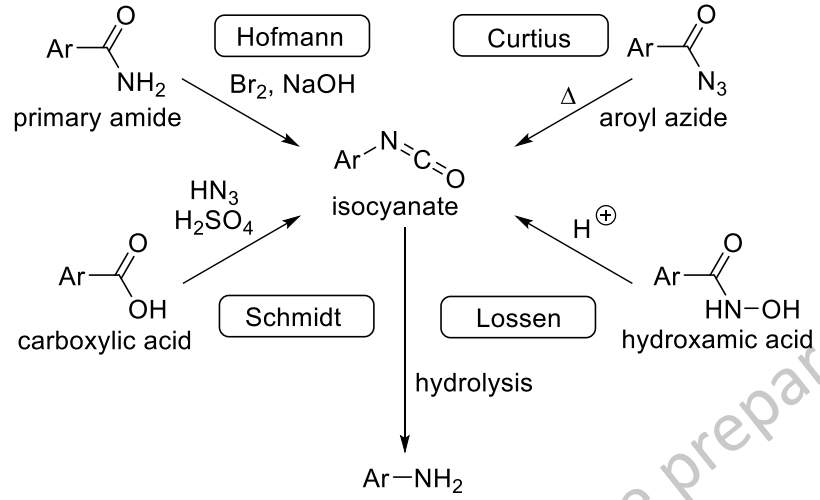
Nitration followed by selective reduction of nitro group leads to the formation of *m*-nitroaniline, while reduction followed by nitration leads to the formation of *p*-nitroaniline.

Accessing amines through rearrangement reactions:

Primary aromatic amines can be prepared by a number of rearrangement reactions that involve migration of an aryl ring from carbon to an electron-deficient nitrogen. We have already discussed these reactions in some detail, so a brief overview is provided here.

The relevant rearrangement reactions are Hofmann amide degradation, Lossen rearrangement, Curtius rearrangement, Schmidt reaction of carboxylic acids and Beckmann rearrangement.

Among these, the first four lead directly to isocyanate derivatives that on hydrolysis reveals the amine, while Beckmann rearrangement gives rise to an amide, which, if required, may be dismantled to get the amine.



Point to be noted that all the substrates of these rearrangement reactions can eventually be traced back to the corresponding carboxylic acid, which, in turn, can be accessed by either of the following methods:

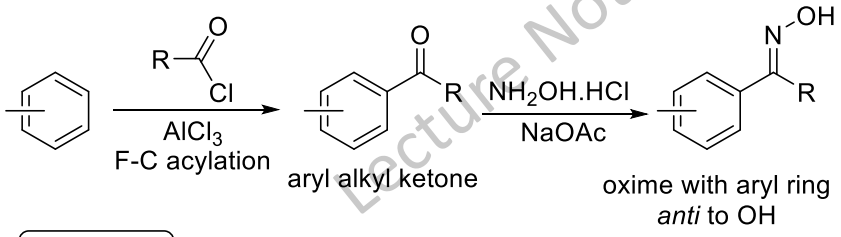
a) side chain oxidation of the corresponding hydrocarbon (toluene to benzoic acid, reagent?),

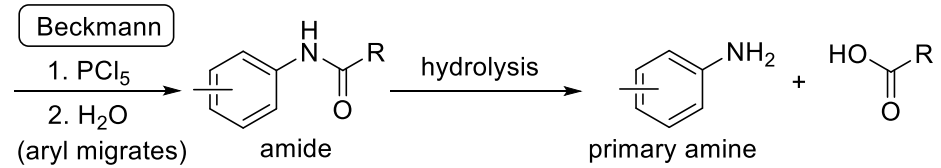
b) Grignard reaction (recall the synthesis of mesitoic acid),

c) haloform reaction of the corresponding methyl ketone (acetophenone to benzoic acid, reagent?), or

d) hydrolysing the corresponding aromatic cyanide compounds (cyanobenzene to benzoic acid, reagent?).

The last technique, though, is not useful here if the aryl cyanide is accessed through the corresponding aromatic amine (which is our ultimate target molecule in this case) via diazotization and subsequent Sandmeyer reaction.





As such, oxime formation would lead to two different diastereomers, if the starting keto compound is unsymmetrical, but point to note that for an aryl alkyl ketone, the major product is that oxime which places the bulkier aromatic ring *anti* to the hydroxyl group. This is advantageous as we need the aryl group to migrate in this case and the stereoelectronic requirement for such a migration is precisely the *anti* arrangement between the migrating group and the hydroxyl-turned-to a leaving group.