

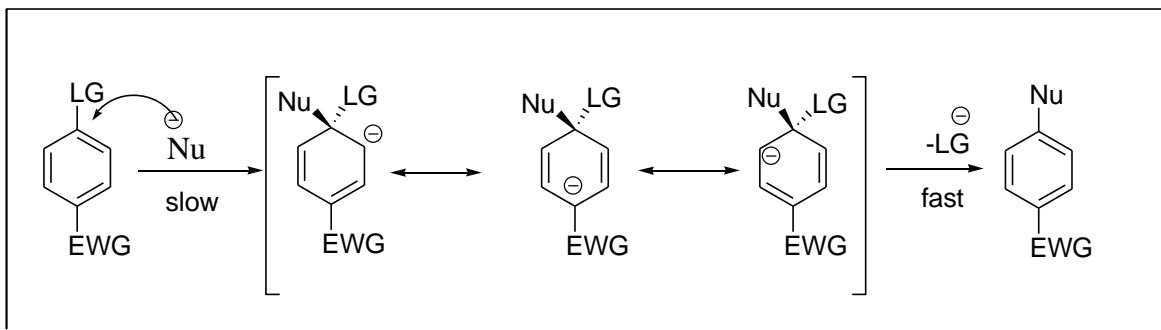
Lecture 15 Aromatic Nucleophilic Substitution

6.1 Principles

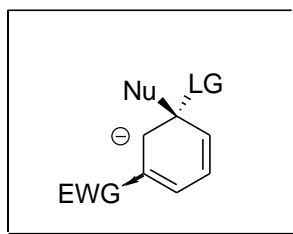
There are four principal mechanisms for aromatic nucleophilic substitution which are similar to that of aliphatic nucleophilic substitution.

6.1.1 S_NAr Mechanism

The introduction of electron withdrawing group (EWG) on the aromatic nucleus makes the system susceptible to nucleophilic attack. The mechanism is similar to that of electrophilic substitution except that an anion rather than a cation intermediate is involved. The nucleophile adds to the aromatic ring to afford a delocalized anion from which the leaving group (LG) is eliminated.

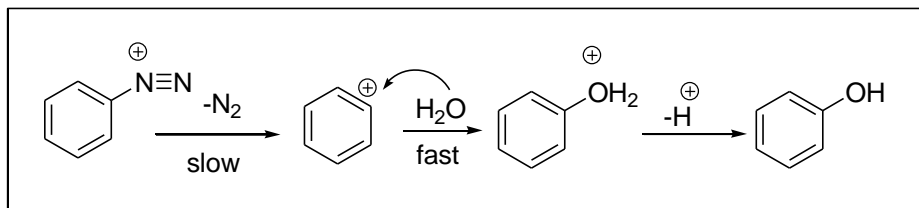


The delocalization of the negative charge can occur only when the nucleophile adds to the *ortho* or *para* position with respect to the EWG. Addition to *meta* position gives an adduct stabilized by the inductive effect, but not the mesomeric effect. Therefore, towards nucleophiles, EWG are activating and *ortho*, *para*-orienting and, in contrast, electron donating group (EDG) deactivating and *meta* directing. These principles are opposite of those that apply to electrophilic substitution.



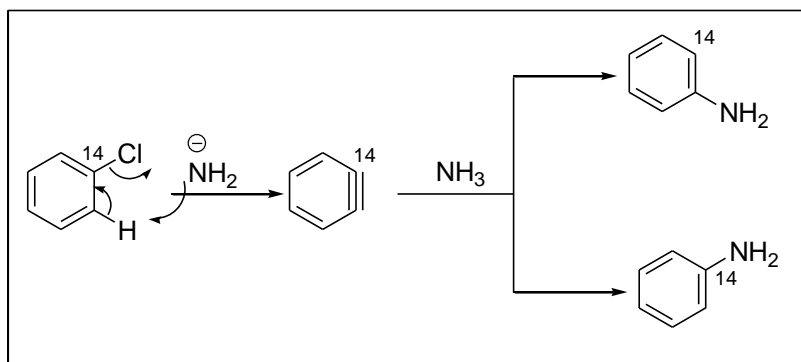
6.1.2 S_N1 Mechanism

This mechanism operates in the reaction of diazonium salts with nucleophiles. The driving force resides in the strength of the bonding in the nitrogen molecule that makes it a particularly good leaving group.



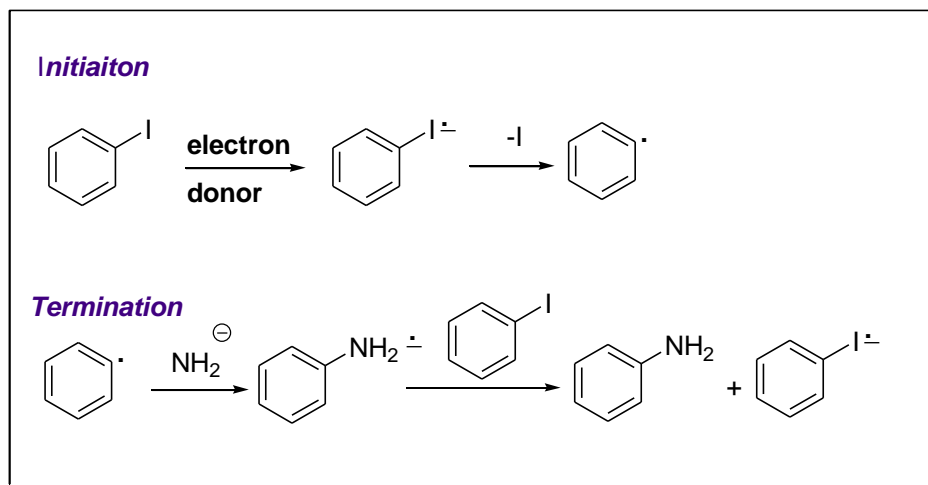
6.1.3 Benzyne Mechanism

Aryl halides that have no activating groups proceed reactions with strong base to give benzyne intermediate which undergoes reaction with nucleophile to give a mixture of regioisomers.



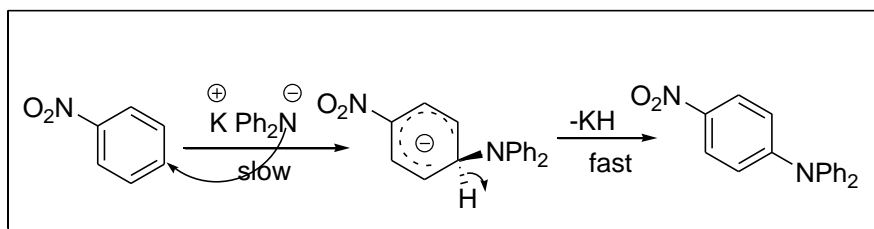
6.1.4 S_{RN}1 Mechanism

S_{RN}1 reactions take place via free-radical intermediate and have wide substrate scope. Besides initiation by solvated electrons, they are also initiated photochemically, electrochemically and even thermally.



6.2 Displacement of Hydride Ion

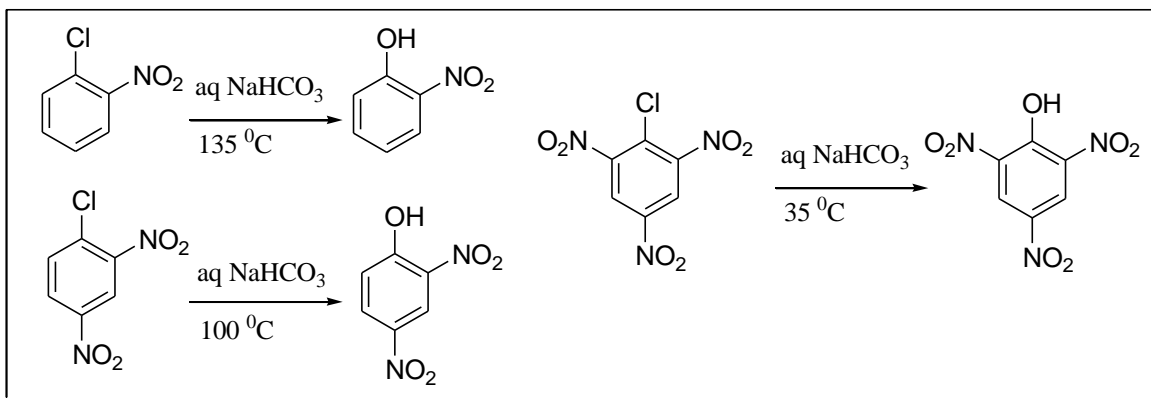
Benzene having EWG such as nitro group reacts with the most reactive nucleophiles such as amide or amide ion by displacement of hydride ion.



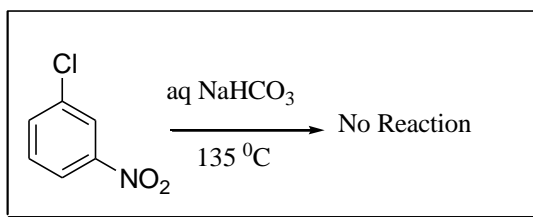
6.3 Displacement of Other Anions

6.3.1 Halides

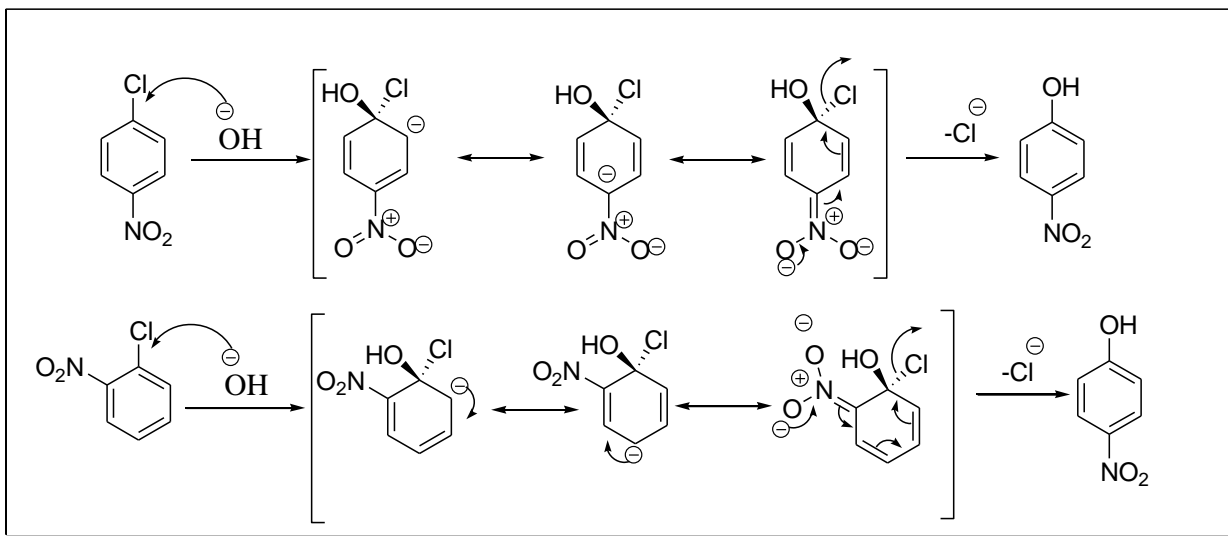
The reactivity of halide increases with increase in number of electron withdrawing groups (Scheme 1). For examples, the reactivity of chlorobenzene having nitro groups towards aqueous NaHCO_3 follows:



However, *m*-nitrochlorobenzene does not undergo similar reaction:

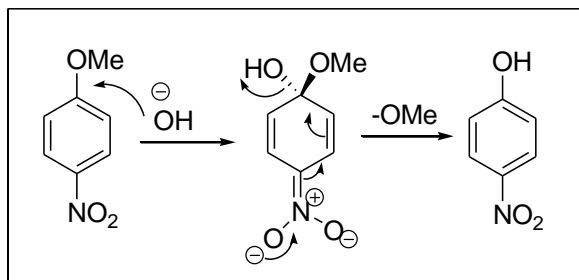


Mechanism



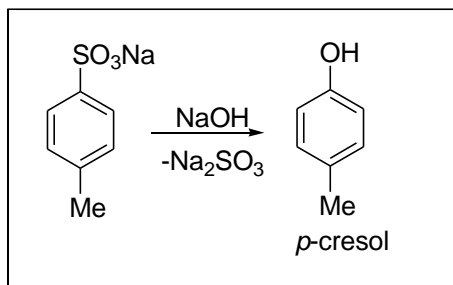
6.3.2 Oxyanions

Aryl ethers bearing EWG in *ortho* and *para* positions proceed hydrolysis to afford phenols.



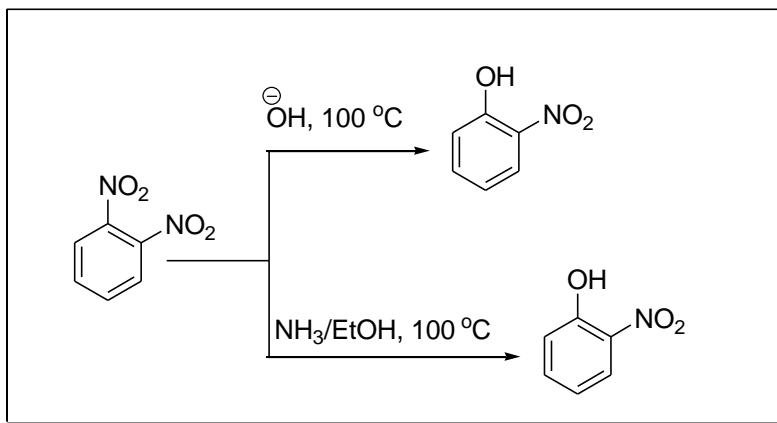
6.3.3 Sulfite Ion

Aryl sulphonic acid can be converted, through their salts, to phenols, by alkali fusion. In spite of the extreme conditions, the reaction gives fairly good yields, except when the substrate contains other groups that are attacked by the alkali at the fusion temperature. Milder conditions can be used when the substrate contains activating groups, but the presence of deactivating groups hinders the reaction. The mechanism is obscured but the benzyne intermediate has been ruled out by the finding that the cine substitution does not occur. For example, sodium *p*-toluenesulfonate with fused sodium hydroxide gives *p*-cresol at 250-300 °C.



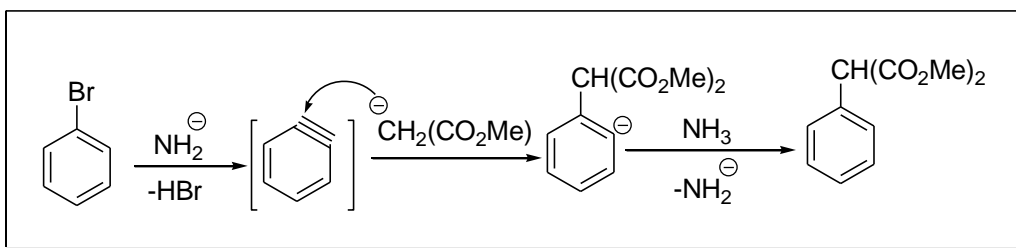
6.3.4 Nitrogen Anions

Nitrite ion could be displaced if other nitro groups are present to activate the aromatic nucleus.

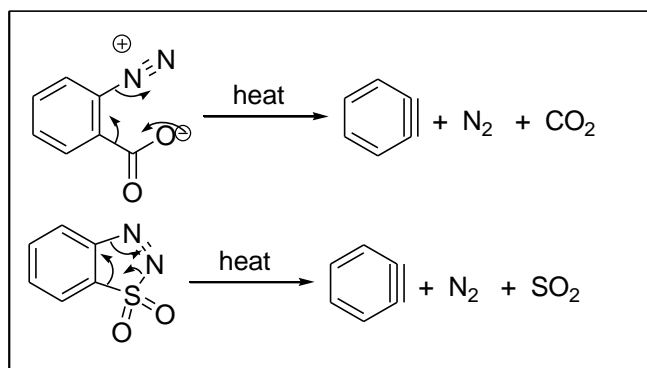


6.4 Substitution via Benzyne

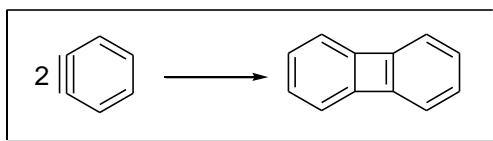
Halobenzenes (except fluorobenzene) directly react with strong base such as sodamide to give benzyne that can be reacted with any nucleophile present in the reaction medium. For example, the addition of malonic ester to liquid ammonia having amide ion affords the corresponding enolate that reacts with benzyne as it is produced.



Furthermore, *ortho* substituted benzenes from which two stable molecules can be generated by elimination afford benzyne on thermolysis.

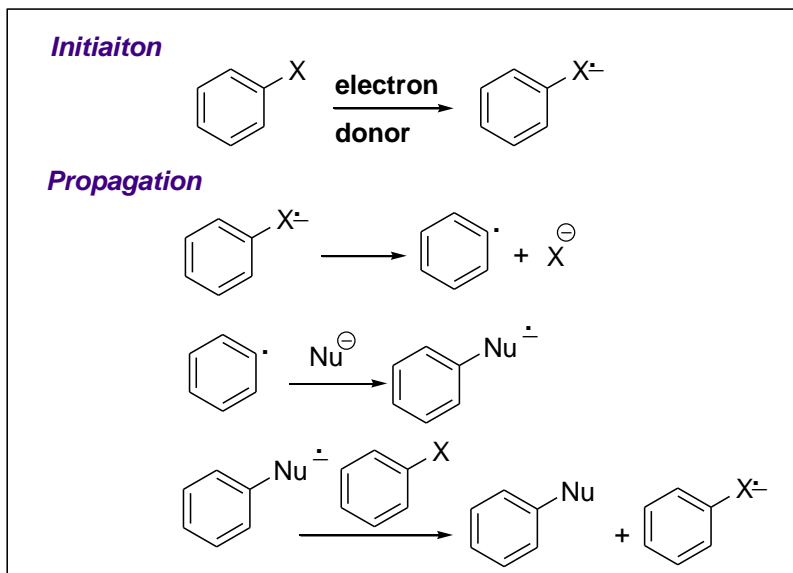


If the nucleophile is not present in the reaction medium, benzyne dimerizes to give biphenylene.

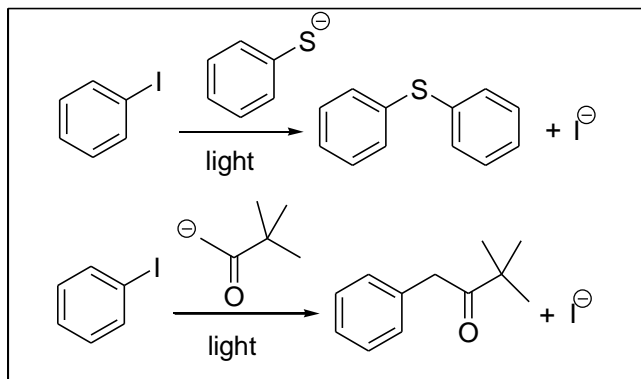


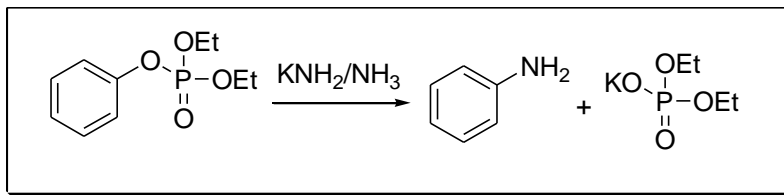
6.5.1 The $S_{RN}1$ Reaction

Unactivated aryl halides proceed nucleophilic substitution with typically enolates, amide ion and thiol anion via a chain reaction involving anion radicals in that the initiation step is an electron transfer. The first two steps are similar to those in S_N1 reaction which led to the designation $S_{RN}I$ (R for radical).



The initiation of the reaction is generally either by solvated electron (sodium in liquid ammonia) or with photochemical excitation in that the nucleophile is the electron donor. For examples,



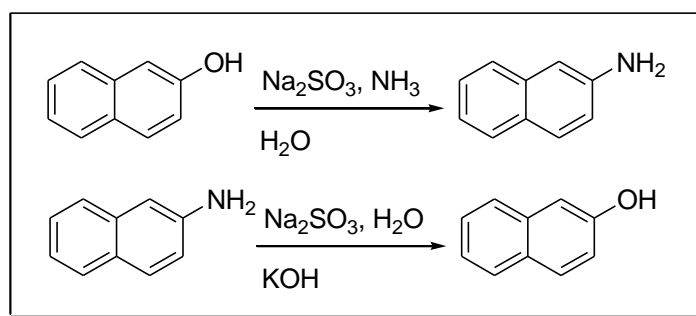


6.5.2 Bucherer Reaction

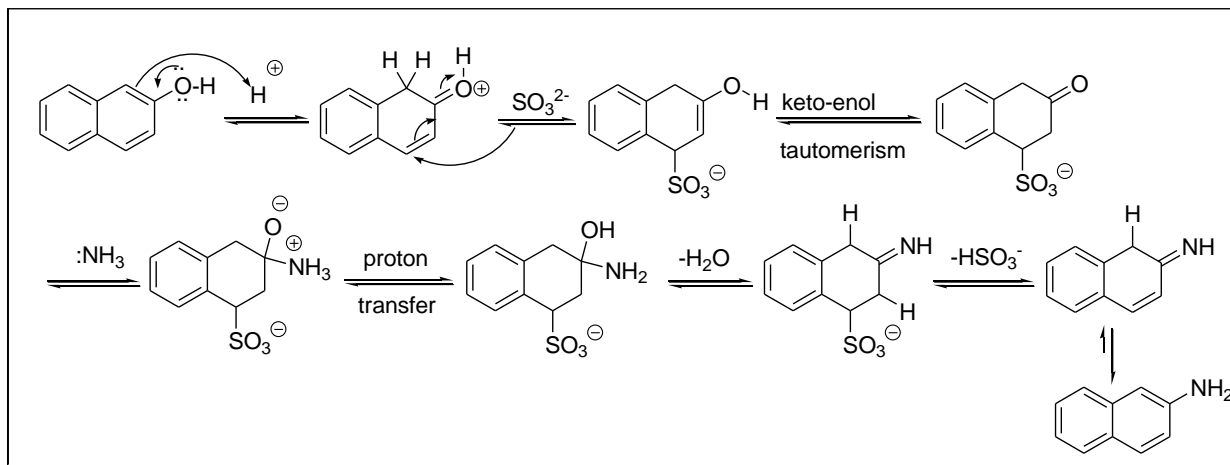
Some phenols proceed reaction with aqueous ammonium nitrite to give aromatic amines.

The reactions are believed to take place via sulfite adduct of the keto-tautomer of phenol.

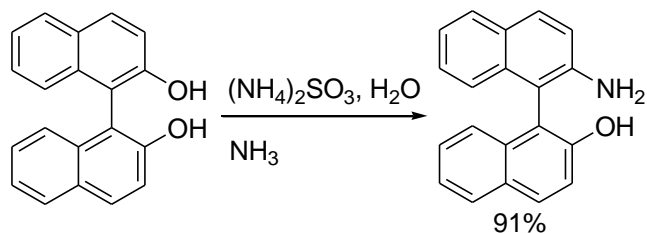
Similarly, certain aromatic amines can be converted into phenols.



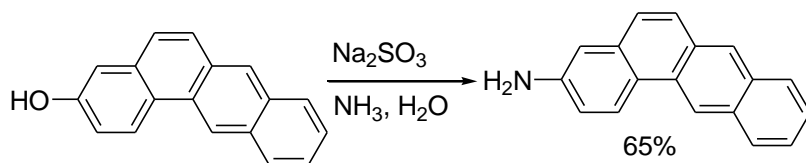
Proposed Mechanism



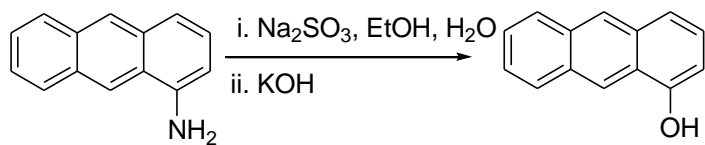
Examples:



K. Korber, W. Tang, X. Hu, *Tetrahedron Lett.* **2002**, 43, 7163.



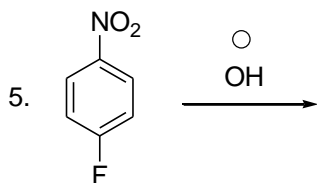
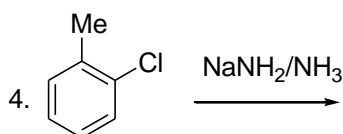
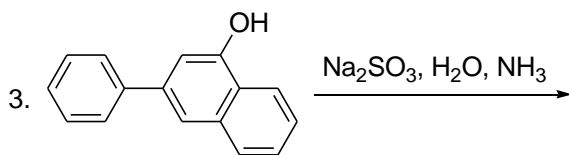
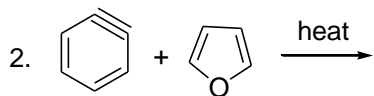
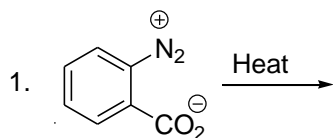
L. F. Fieser, E. B. Hershberg, L. Long, Jr., M. S. Newman, *J. Am. Chem. Soc.* **1937**, 59, 475. ,



R. S. Coleman, M. A. Mortensen, *Tetrahedron Lett.* **2003**, 44, 1215.

Problems:

Provide the major products with mechanistic rationale for the following reactions.



Text Books:

R.O.C. Norman and C. M. Coxon, *Principles of Organic Synthesis*, CRC Press, New York, 2009.

B. P. Mundy, M. G. Eller, F. G. Favaloro Jr, *Name Reactions and Reagents in Organic Synthesis*, Wiley Interscience, New Jersey, 2005.