Organic Chemistry-4

Semester-4, CBCS

Course: CEMA CC-4-8-TH

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Organonitrogen Chemistry

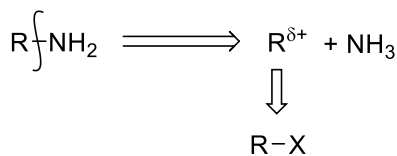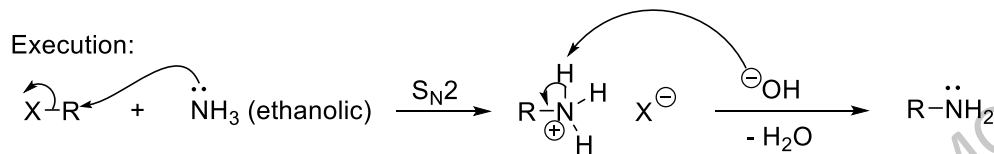Chemistry of amines: Synthesis of aliphatic amines: Let us consider the synthesis of the primary amine $R-NH_2$. Forming a C-N (carbon-heteroatom) bond is easier than forming a C-C bond.
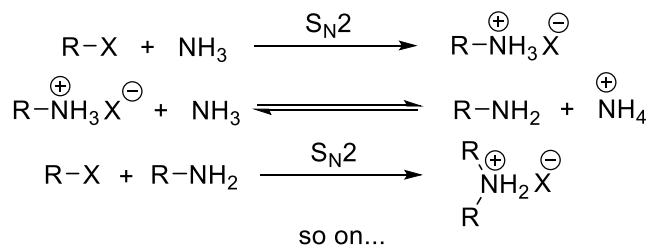
Proposal:

Execution:

Limitation in implementation:

$$R-X + NH_3 \xrightarrow{S_N2} R-\overset{\oplus}{N}H_3 \overset{\ominus}{X}$$

$$R-\overset{\oplus}{N}H_3\overset{\ominus}{X} + NH_3 \rightleftharpoons R-NH_2 + \overset{\oplus}{N}H_4$$

$$R-X + R-NH_2 \xrightarrow{S_N2} \overset{R}{\underset{R}{\overset{\oplus}{N}H_2}}\overset{\ominus}{X}$$

so on...

Products of each alkylation is capable of acting as nucleophiles. Overalkylation leading to mixture of products is a serious problem.

After final alkali treatment we get a mixture of RNH_2, R_2NH, R_3N and R_4N^+.

Way out?

O. H. D. Hinsberg
(1857-1939)

One (crude) solution: Hinsberg's separation:
rescuing the individual amines from the mixture:

p-toluenesulfonyl chloride;
TsCl
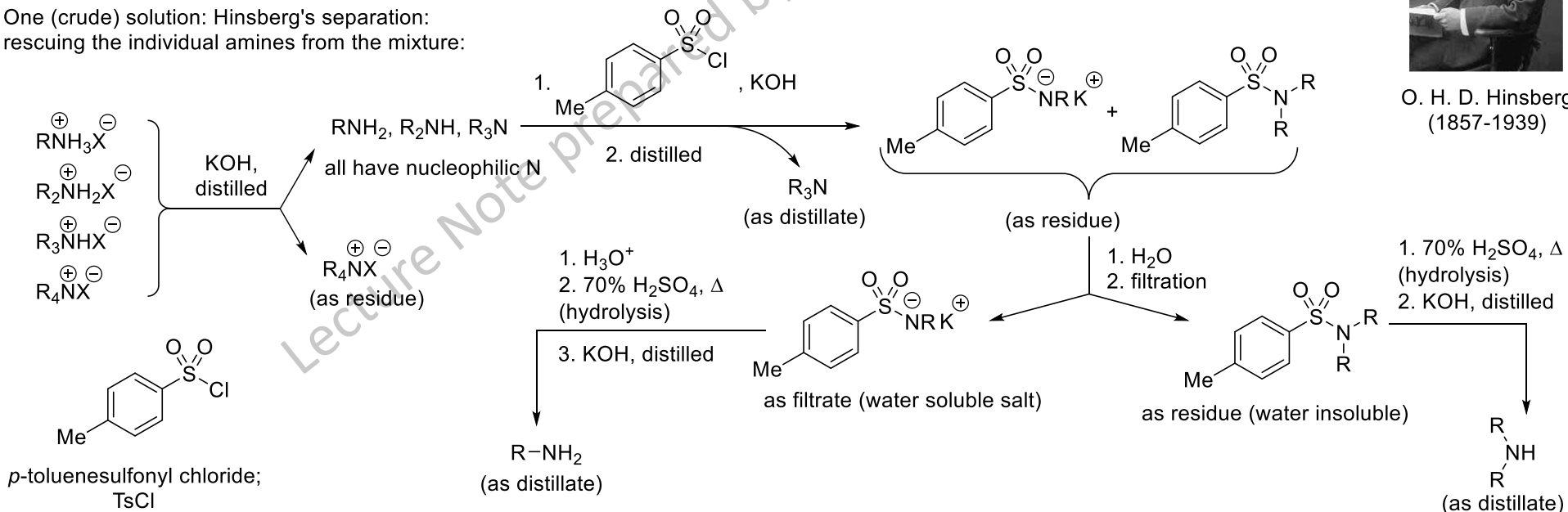
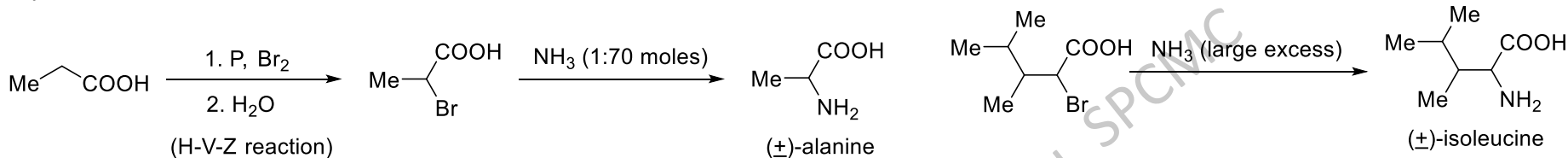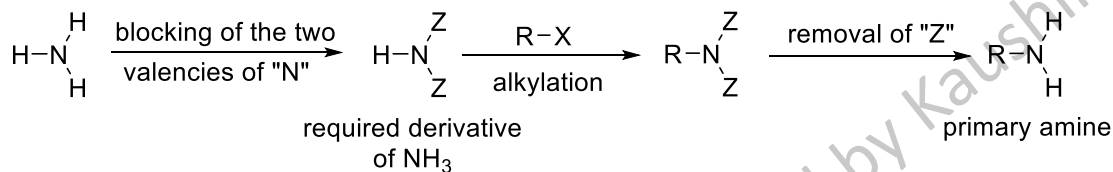**Organonitrogen Chemistry**

Trying to synthesise RNH$_2$ exclusively:

[A] As evident from the scheme shown previously, here NH$_3$, RNH$_2$, R$_2$NH, and R$_3$N are in competition to react with RX. If NH$_3$ acts as the nucleophile in preference over the other nucleophilic species, we may get the primary amine. So we have to use a *large excess* of NH$_3$. Thus we have the following ways to obtain amino acids:
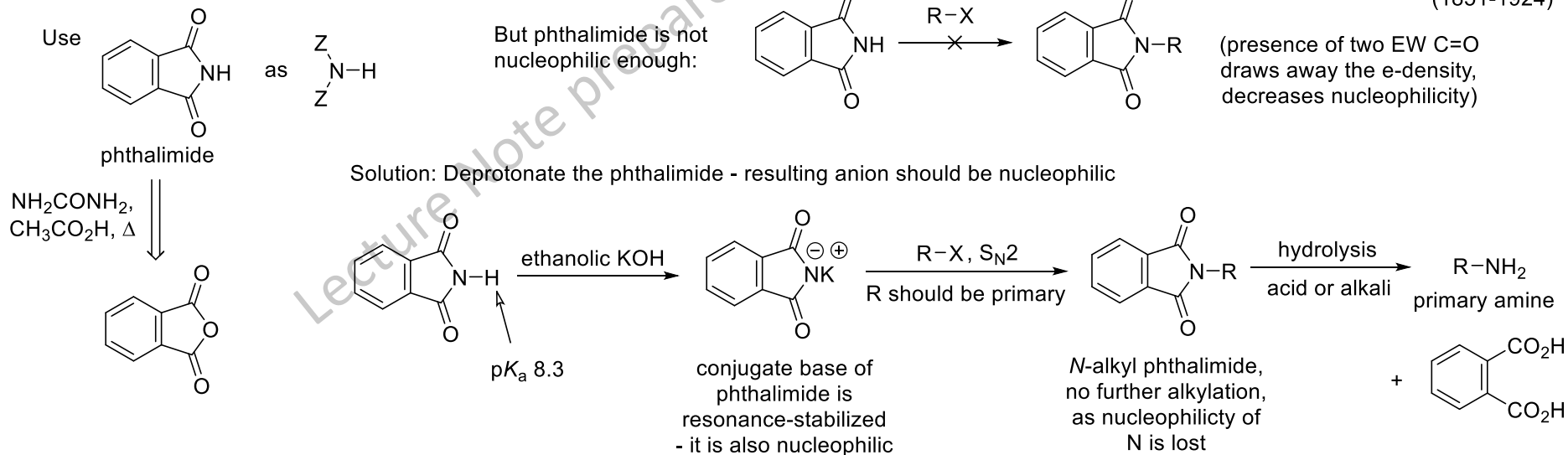

Me—CH$_2$—COOH $\xrightarrow[\text{2. H}_2\text{O}]{\text{1. P, Br}_2}$ (H-V-Z reaction)

(±)-alanine

(±)-isoleucine

[B] Use a masked form of ammonia in which two valences of nitrogen are satisfied by easily removable groups, i.e.

required derivative of NH$_3$
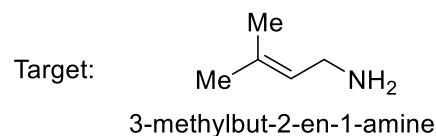
primary amine

S. Gabriel
(1851-1924)

Gabriel's phthalimide synthesis:

Use phthalimide as

But phthalimide is not nucleophilic enough:

(presence of two EW C=O draws away the e-density, decreases nucleophilicity)

NH$_2$CONH$_2$, CH$_3$CO$_2$H, Δ

Solution: Deprotonate the phthalimide - resulting anion should be nucleophilic

$\xrightarrow{\text{ethanolic KOH}}$ $\xrightarrow[\text{R should be primary}]{\text{R}-\text{X, S}_N2}$ $\xrightarrow[\text{acid or alkali}]{\text{hydrolysis}}$ R—NH$_2$

primary amine

pK$_a$ 8.3

conjugate base of phthalimide is resonance-stabilized - it is also nucleophilic

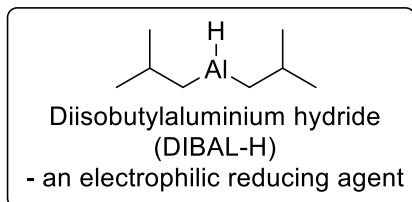*N*-alkyl phthalimide, no further alkylation, as nucleophilicty of N is lost

Organonitrogen Chemistry

Example of Gabriel synthesis:

Target:

3-methylbut-2-en-1-amine
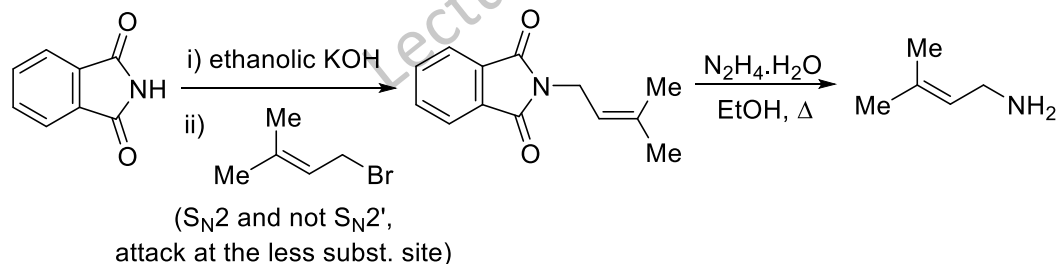
Retrosynthetic analysis:

Synthesis:

Liberating the amine from the *N*-alkylphthalimide:

The acidic or alkaline hydrolysis of *N*-alkylphthalimide is a slow reaction. However, the primary amine can be released from *N*-alkylphthalimide more efficiently by the treatment with hydrazine hydrate. Consider the two approaches:
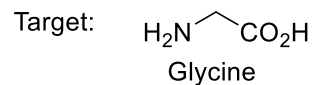
A) Alkaline hydrolysis of N-alkylphthalimide:

B) Hydrazinolysis of N-alkylphthalimide (Ing-Manske procedure):

phthalhydrazide
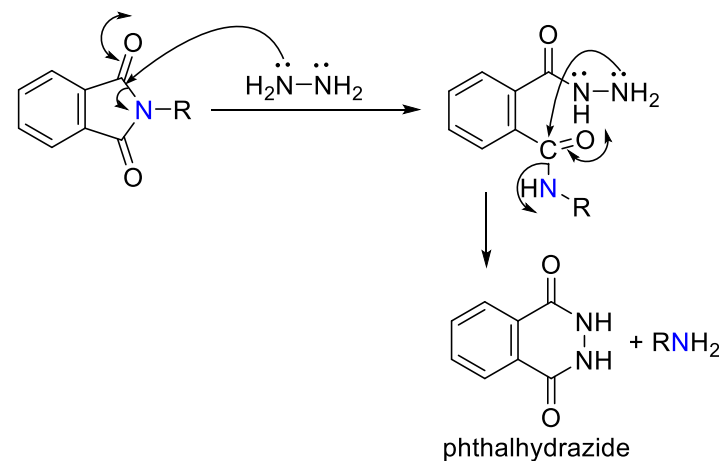
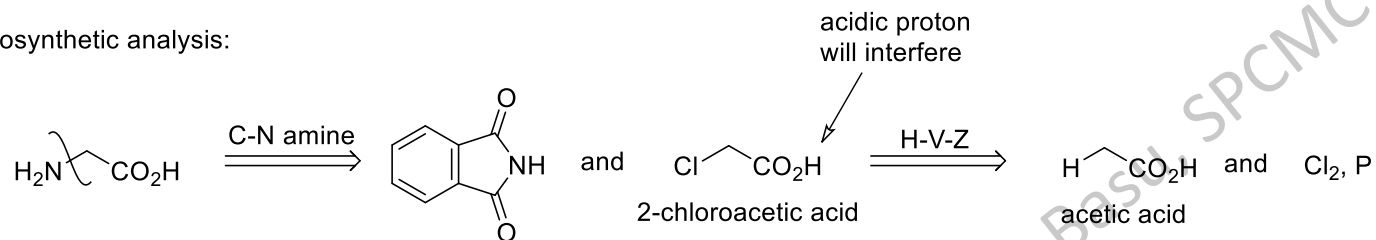Hydrazinolysis of N-alkylphthalimide proceeds more easily than hydrolysis of the same, because

o Hydrazinolysis is entropically more favourable than hydrolysis as the second step for the former is intramolecular in nature.
o Hydrazine is more nucleophilic in nature because of the α-effect.
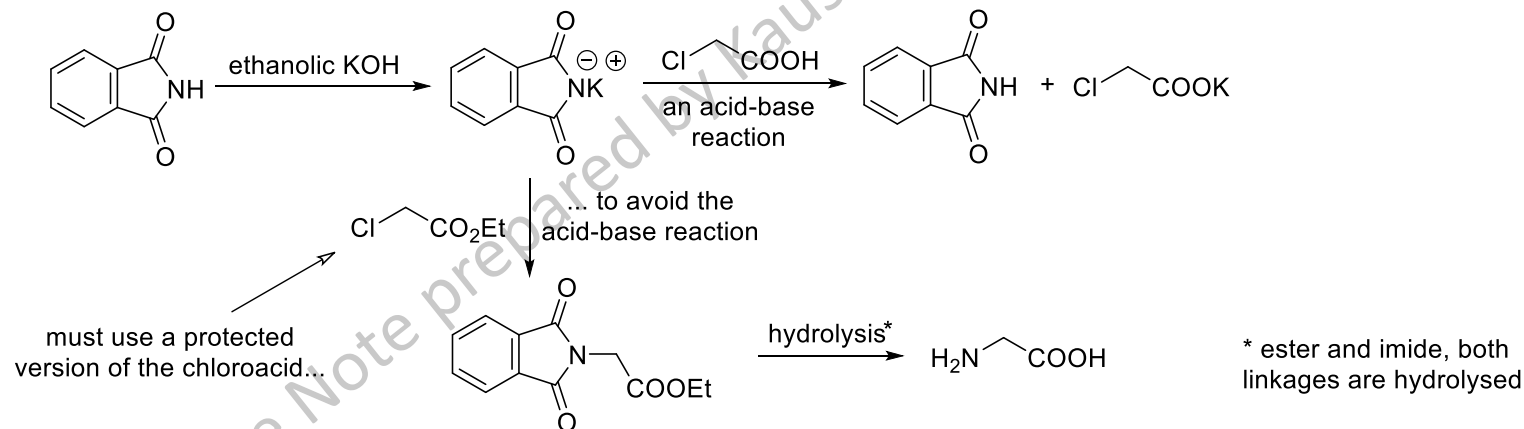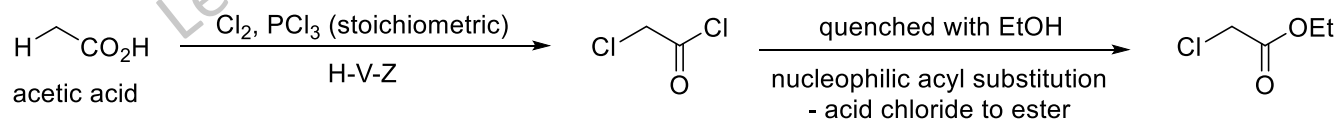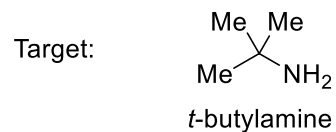
Organonitrogen Chemistry

Example of Gabriel synthesis:

Target:

H_2N CO_2H

Glycine

Retrosynthetic analysis:

acidic proton will interfere

H_2N CO_2H $\xrightarrow{\text{C-N amine}}$ phthalimide (NH) and Cl CO_2H $\xrightarrow{\text{H-V-Z}}$ H CO_2H and Cl_2, P

2-chloroacetic acid   acetic acid

Synthesis:

phthalimide (NH) $\xrightarrow{\text{ethanolic KOH}}$ phthalimide $\overset{\ominus}{N}\overset{\oplus}{K}$ $\xrightarrow[\text{an acid-base reaction}]{Cl\text{—}COOH}$ phthalimide (NH) + Cl $COOK$

Cl CO_2Et

... to avoid the acid-base reaction

must use a protected version of the chloroacid...

phthalimide N—$COOEt$ $\xrightarrow{\text{hydrolysis*}}$ H_2N $COOH$ * ester and imide, both linkages are hydrolysed

Protecting the COOH and functionalising the α-position:

H CO_2H $\xrightarrow[\text{H-V-Z}]{Cl_2, PCl_3 \text{ (stoichiometric)}}$ Cl $\overset{Cl}{\underset{O}{\text{C}}}$ $\xrightarrow[\substack{\text{nucleophilic acyl substitution} \\ \text{- acid chloride to ester}}]{\text{quenched with EtOH}}$ Cl $\overset{OEt}{\underset{O}{\text{C}}}$

acetic acid

Organonitrogen Chemistry
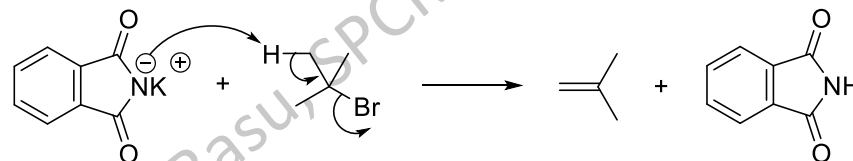
Faliure of Gabriel's synthesis:

Target:

Me Me
|
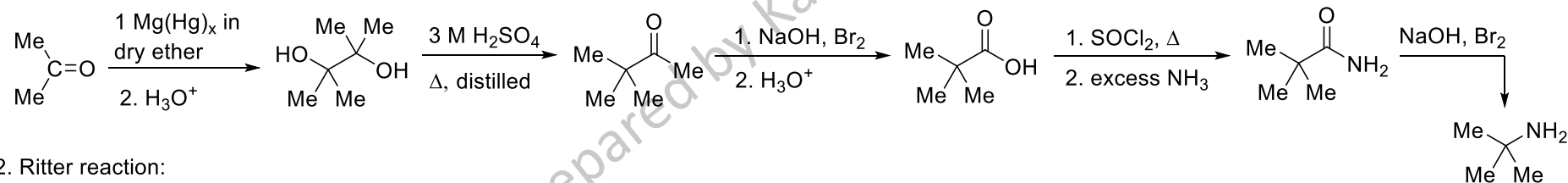Me—C—NH₂

t-butylamine

Retrosynthetic analysis:
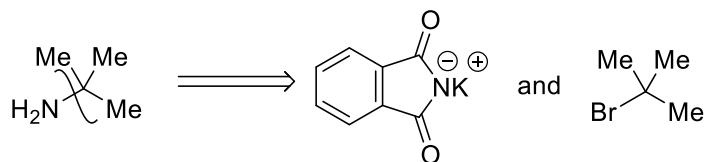
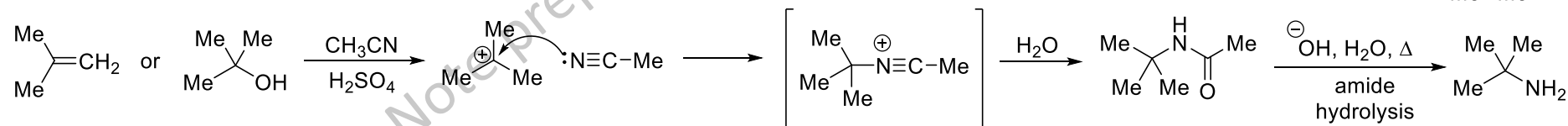Problem: with a tertiary amine, elimination takes over:

Gabriel's synthesis will fail here.

Way out?
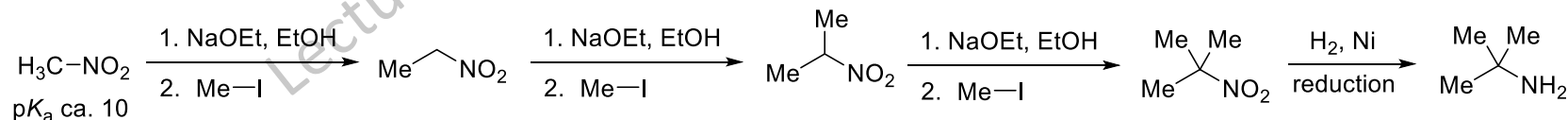
1. Recall that compounds containing the *t*-butyl group can be accessed via the Pinacol-Pinacolone rearrangement.
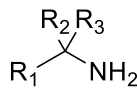

2. Ritter reaction:

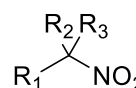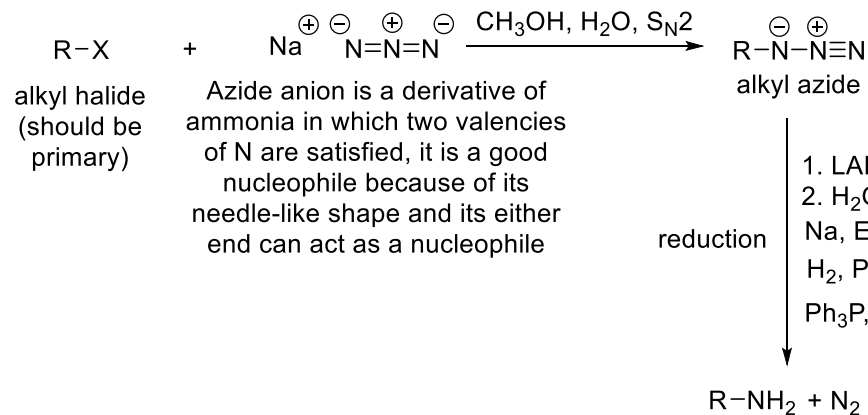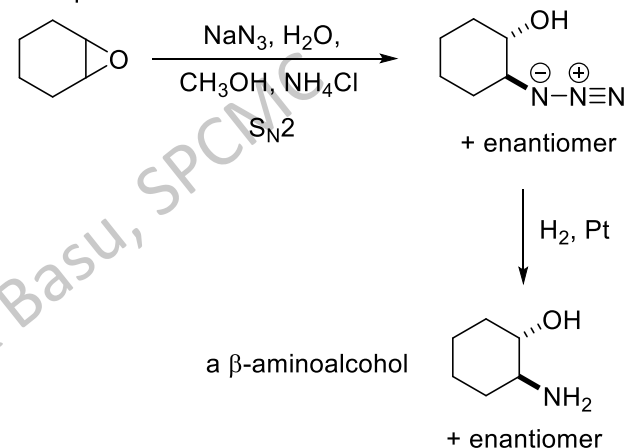3. Exploiting the acidity of nitromethane:

H_3C-NO_2
pK_a ca. 10

We can access

$$\begin{array}{c} R_2 \ R_3 \\ R_1-C-NH_2 \end{array}$$

from

$$\begin{array}{c} R_2 \ R_3 \\ R_1-C-NO_2 \end{array}$$

which, in turn, can be made from H_3C-NO_2

Organonitrogen Chemistry

Synthesis of primary amines: using ammonia derivatives with two valencies blocked by removable groups (contd.)

R−X + Na $\overset{\oplus}{}$ $\overset{\ominus}{N}$=$\overset{\oplus}{N}$=$\overset{\ominus}{N}$ $\xrightarrow{\text{CH}_3\text{OH, H}_2\text{O, S}_N2}$ R−$\overset{\ominus}{N}$−$\overset{\oplus}{N}$≡N

alkyl halide (should be primary)

Azide anion is a derivative of ammonia in which two valencies of N are satisfied, it is a good nucleophile because of its needle-like shape and its either end can act as a nucleophile

alkyl azide

reduction

1. LAH, dry ether,
2. H$_2$O, or
Na, EtOH, or
H$_2$, Pt, or
Ph$_3$P, H$_2$O

R−NH$_2$ + N$_2$

Example:

$\xrightarrow[\text{CH}_3\text{OH, NH}_4\text{Cl} \quad S_N2]{\text{NaN}_3, \text{H}_2\text{O},}$

...OH
$\overset{\ominus}{N}$−$\overset{\oplus}{N}$≡N

+ enantiomer

$\downarrow$ H$_2$, Pt

OH
NH$_2$

a β-aminoalcohol

+ enantiomer
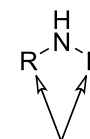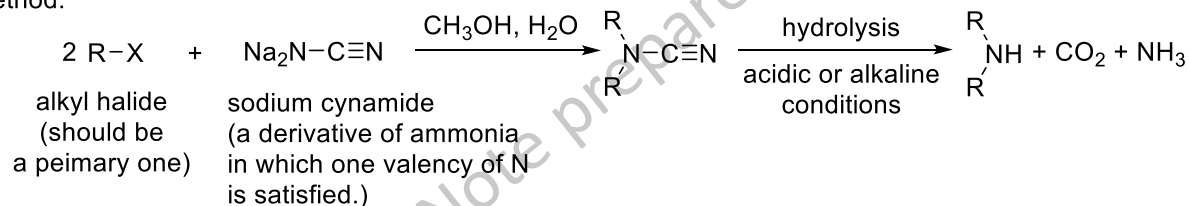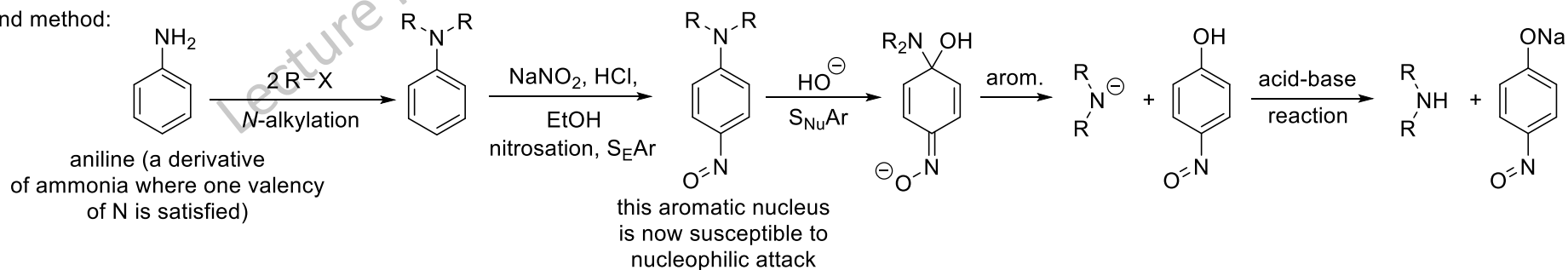
By analogy with the synthesis of primary amines using phthalimide or sodium azide, secondary amines can be accessed by using an ammonia derivative where only one of the three valencies of nitrogen is satisfied by an easily removable group.

First method:

2 R−X + Na$_2$N−C≡N $\xrightarrow{\text{CH}_3\text{OH, H}_2\text{O}}$ $\overset{R}{\underset{R}{N}}$−C≡N $\xrightarrow[\text{acidic or alkaline conditions}]{\text{hydrolysis}}$ $\overset{R}{\underset{R}{N}}$H + CO$_2$ + NH$_3$

alkyl halide (should be a peimary one)

sodium cynamide (a derivative of ammonia in which one valency of N is satisfied.)

R−N−R (three-membered ring)

same alkyl group on N avoiding the overalkylation problem

Second method:

NH$_2$ $\xrightarrow[\text{N-alkylation}]{\text{2 R−X}}$ $\overset{R}{\underset{}{N}}$R $\xrightarrow[\text{EtOH nitrosation, S}_E\text{Ar}]{\text{NaNO}_2, \text{HCl,}}$ $\overset{R,R}{N}$ ... O=N $\xrightarrow[\text{S}_{Nu}\text{Ar}]{\text{HO}^{\ominus}}$ R$_2$N OH ... $\overset{\ominus}{}$O−N $\xrightarrow{\text{arom.}}$ $\overset{R}{\underset{R}{N}}{}^{\ominus}$ + OH ... O=N $\xrightarrow[\text{reaction}]{\text{acid-base}}$ $\overset{R}{\underset{R}{N}}$H + ONa ... O=N

aniline (a derivative of ammonia where one valency of N is satisfied)
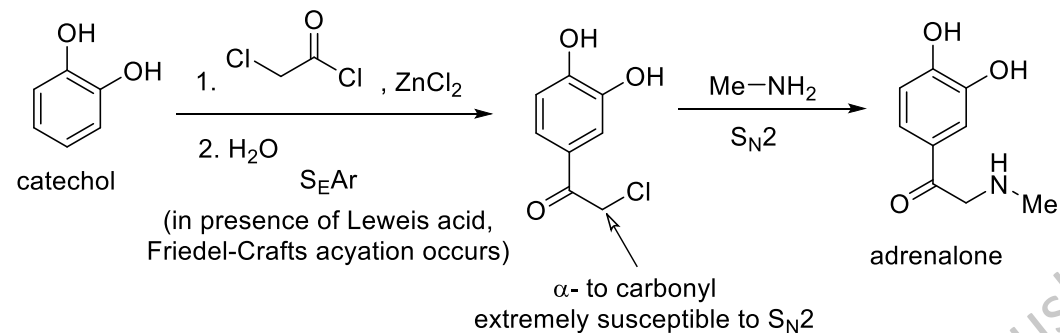
this aromatic nucleus is now susceptible to nucleophilic attack

Organonitrogen Chemistry

Synthesis of secondary and tertiary amines: Alkylation of primary or secondary amines - need to avoid the overalkylation problem:
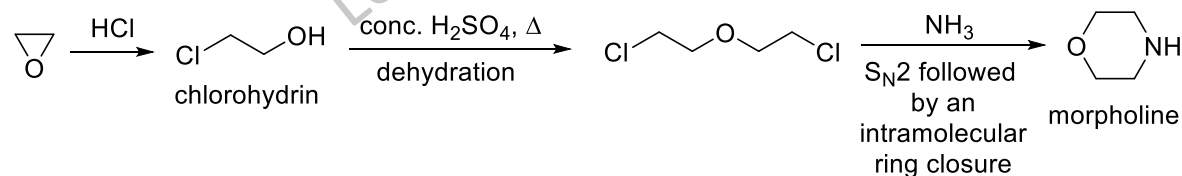
This approach is only useful in cases where the product is less nucleophilic than the starting material (for electronic or steric reasons) or if the alkylation is intramolecular in nature.

catechol

(in presence of Leweis acid, Friedel-Crafts acyation occurs)

S_EAr

α- to carbonyl
extremely susceptible to S_N2

S_N2

adrenalone

The product (a secondary amine) is less nucleophilic than the starting material (methylamine) due to the electron withdrawing -I effect of the neighbouring carbonyl group.

α- to carbonyl
extremely susceptible to S_N2

S_N2

steps

Salbutamol - a drug for asthma
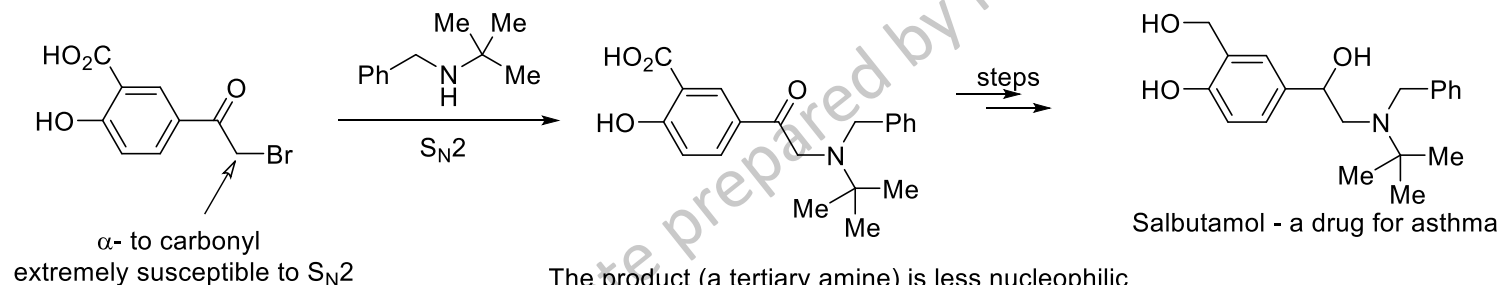
The product (a tertiary amine) is less nucleophilic than the starting material (a secondary amine) due to the -I effect of the neighbouring carbonyl group and also due to steric crowding in the tertiary amine.

HCl

chlorohydrin

conc. H_2SO_4, Δ
dehydration

NH_3
S_N2 followed by an intramolecular ring closure

morpholine

The final product is formed here through an intramolecular reaction which is much faster and more favourable than the competing intermolecular reaction.
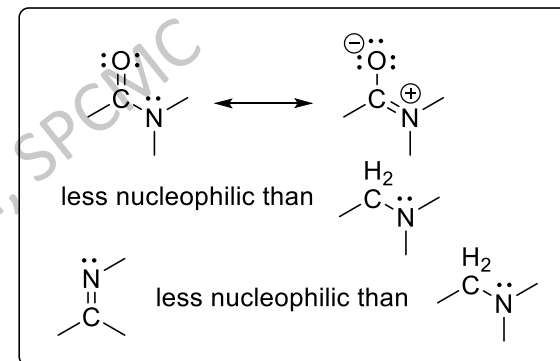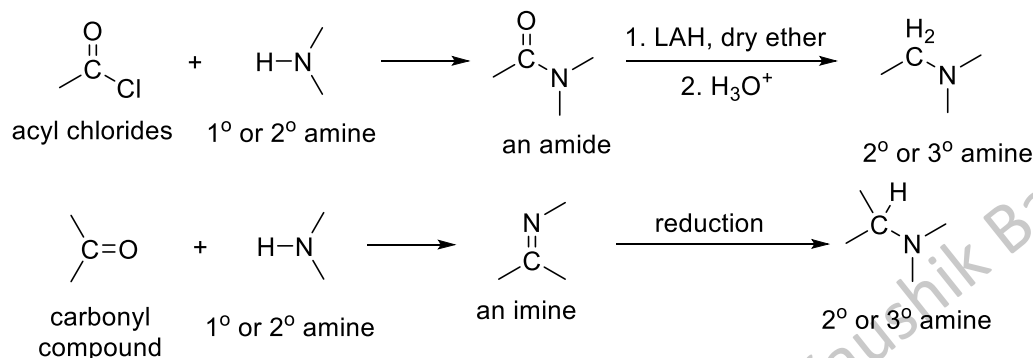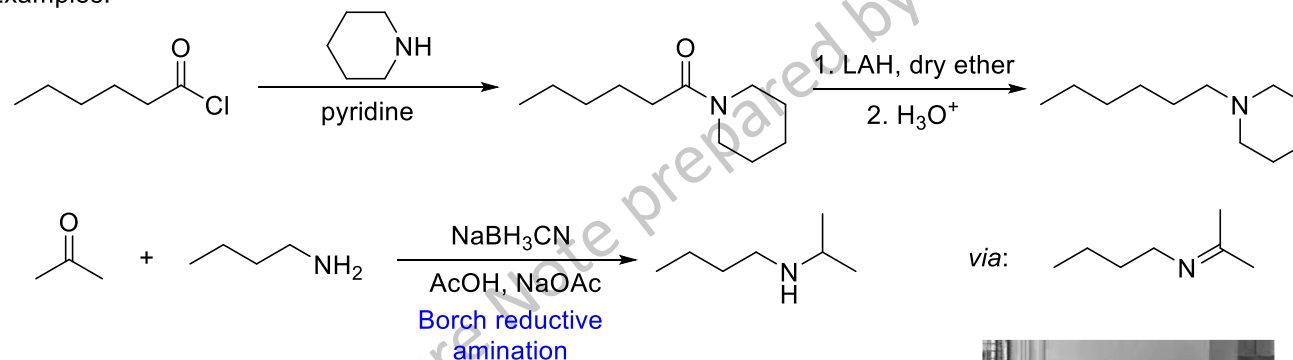
Organonitrogen Chemistry

General protocol for synthesis of secondary and tertiary amines: using electrophiles other than alkyl halides

To avoid the overalkylation problem we can use electrophiles other than alkyl halides which give relatively unreactive products with amines. The best examples are acyl halides, aldehydes and ketones in place of alkyl halides. The products of these reactions, the amides and the imines, are in higher oxidation states than the amine, so they must be reduced to get to the target amines.


acyl chlorides   1° or 2° amine   an amide   2° or 3° amine   less nucleophilic than

carbonyl compound   1° or 2° amine   an imine   2° or 3° amine   less nucleophilic than

Examples:

pyridine   1. LAH, dry ether   2. H₃O⁺

2° or 3° amine   an amide

1° or 2° amine

2° or 3° amine   an imine

1° or 2° amine

NaBH₃CN
AcOH, NaOAc
Borch reductive amination

via:

Sodium cyanoborohydride is an acid-stable variant of sodium borohydride. Alternatively, NaBH(OAc)₃ could be used.

Careful control of the pH of the medium is necessary though and the ideal pH is ca. 6 to 7. At this pH the imine is protonated while the carbonyl is not, thus, only C=N is reduced by hydride transfer.
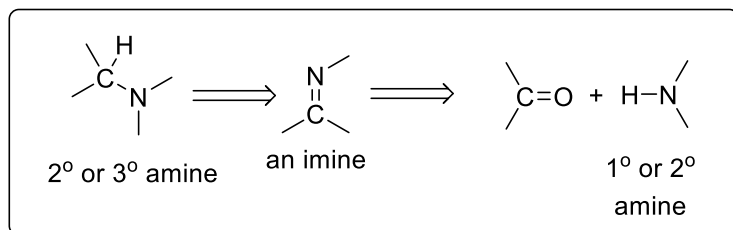
At pH 3 to 4, C=O becomes protonated, and the reducing agent rapidly reacts with the precursor carbonyl instead of the imine.

R. F. Borch
(1941-)
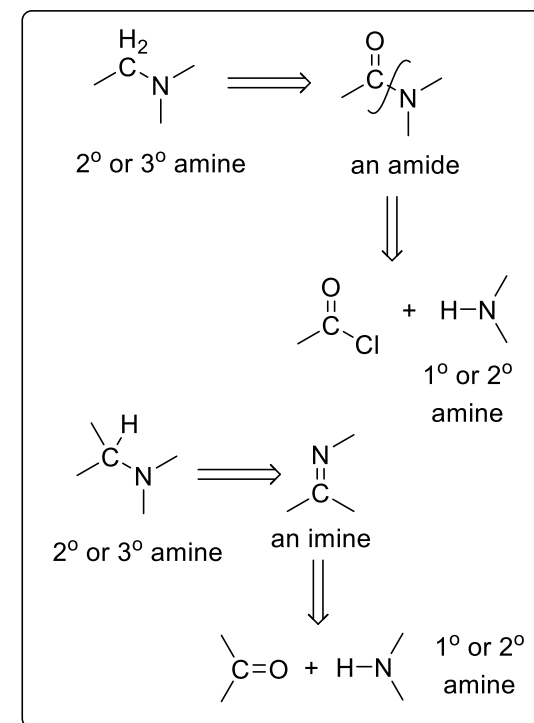
Organonitrogen Chemistry

General protocol for synthesis of secondary and tertiary amines: using electrophiles other than alkyl halides

2° or 3° amine   an imine   1° or 2° amine

Imines are best reduced under acid-catalyzed conditions. Thus the imine route is again suitable for methylation of amines using formaldehyde as the carbonyl component.


Eschweiler-Clarke Methylation
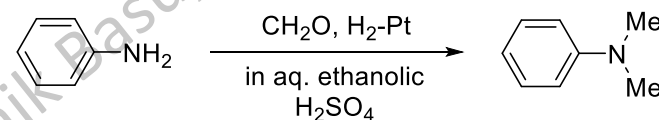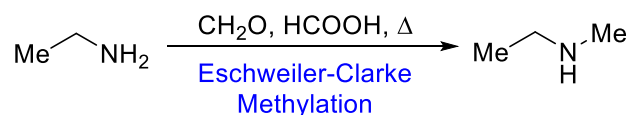
Through Eschweiler-Clarke reductive methylation, a primary amine is converted to a secondary or a tertiary amine and a secondary amine is converted to a tertiary amine by the treatment with formaldehyde in formic acid.

Instead of formic acid, we can use other reducing methods, like catalytic hydrogenation.
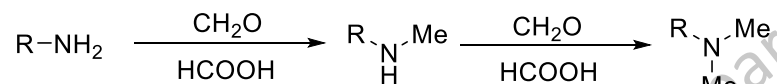
The first methylation of the amine begins with imine formation with formaldehyde. The formic acid acts as a source of hydride and reduces the imine via the intermediate formation of iminium ion to a secondary amine. The driving force is the formation of the gaseous carbon dioxide. Formation of the tertiary amine is similar, but slower due to the difficulties in iminium ion formation.
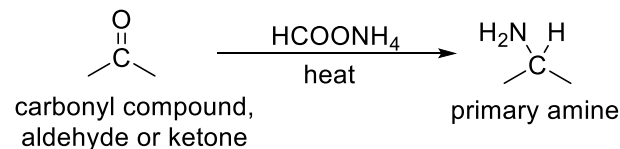

iminium
- hydride acceptor

formate
- hydride donor
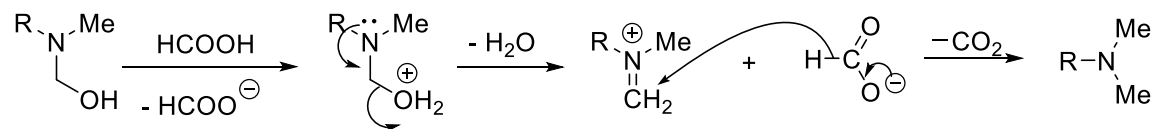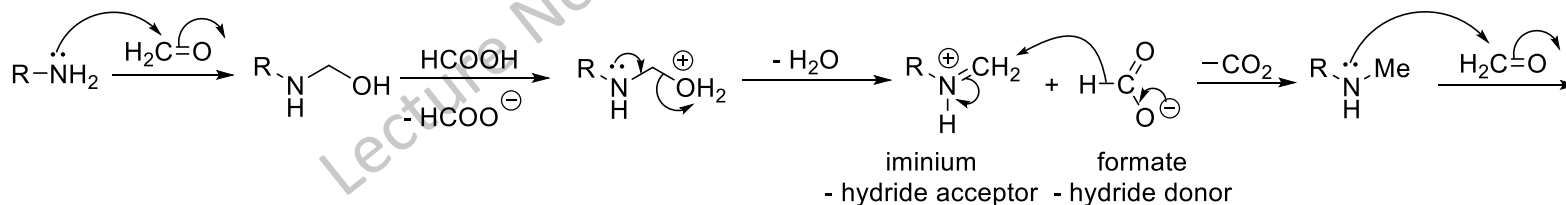
H. T. Clarke
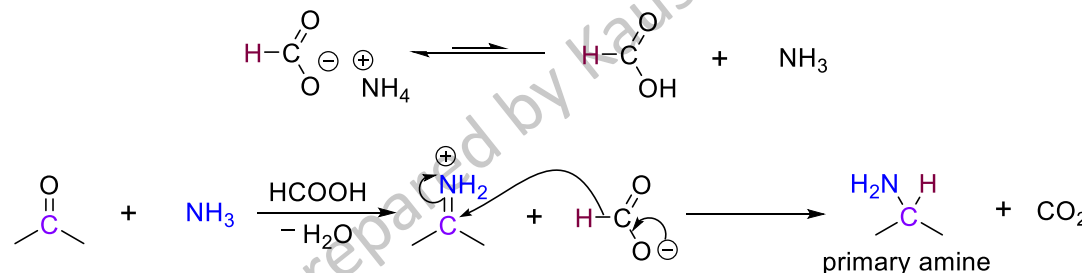(1887-1972)

Organonitrogen Chemistry

Reductive alkylation using ammonia: A route to primary amines?

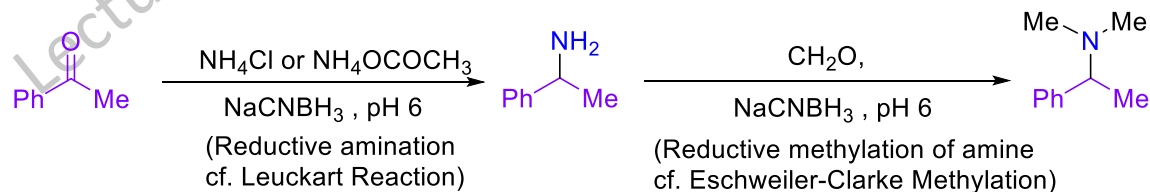We may speculate that the reductive alkylation of ammonia, if possible, should lead to a primary amine.

Leuckart reaction (aka Leuckart-Wallach reaction), analogous to Eschweiler-Clarke methylation:

carbonyl compound,
aldehyde or ketone → primary amine

Otto Wallach
(1847-1941)

Ammonium formate first dissociates into formic acid and ammonia. Ammonia then reacts with the carbonyl compound to form an iminium ion under the acidic condition. Hydride transfer from the formate then reduces the intermediate iminium ion to form an amine and carbon dioxide.

We have already encountered sodium cyanoborohydride, the acid-stable version of the more common reducing agent sodium borohydride. Thus we have the following sequence of reactions:


NH_4Cl or NH_4OCOCH_3

$NaCNBH_3$, pH 6

(Reductive amination
cf. Leuckart Reaction)

CH_2O,

$NaCNBH_3$, pH 6

(Reductive methylation of amine
cf. Eschweiler-Clarke Methylation)
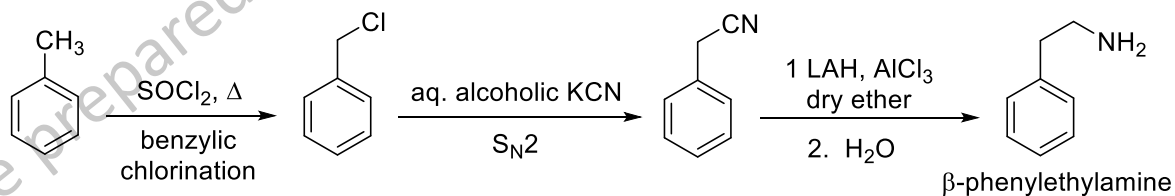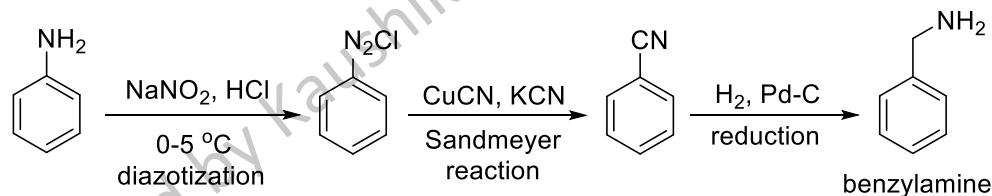
Organonitrogen Chemistry

Reductive alkylation using ammonia: A route to primary amines *via* primary amides and cyanides

The reductive alkylation of ammonia via the intermediate formation of primary amide can be used to obtain primary amine also.

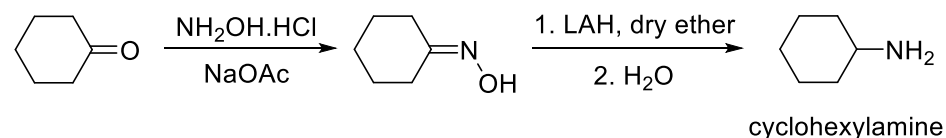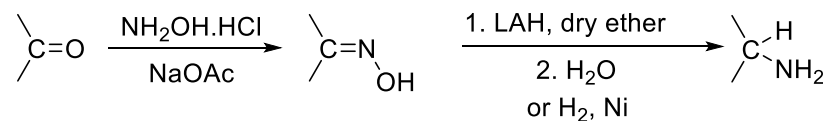trimethylacetic acid → neopentylamine
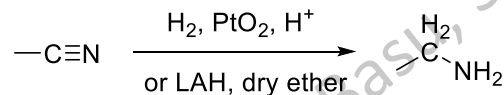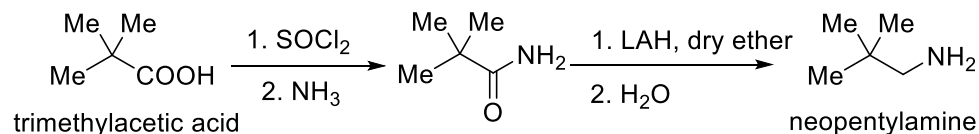
A better method is reducing cyanides
(although this does not work for synthesis of neopentylamine)

Especially suitable for benzyl amines since aryl cyanides can be made from diazonium salts through Sandmeyer reaction and for the homologous amines since cyanide ion reacts easily with benzyl halides.

NaNO$_2$, HCl / 0-5 °C / diazotization → CuCN, KCN / Sandmeyer reaction → H$_2$, Pd-C / reduction → benzylamine

SOCl$_2$, Δ / benzylic chlorination → aq. alcoholic KCN / S$_N$2 → 1 LAH, AlCl$_3$ dry ether / 2. H$_2$O → β-phenylethylamine

A much better method analogous to the above concept is the reduction of oximes which are more stable intermediates than imines and can be accessed from corresponding carbonyl compounds easily:
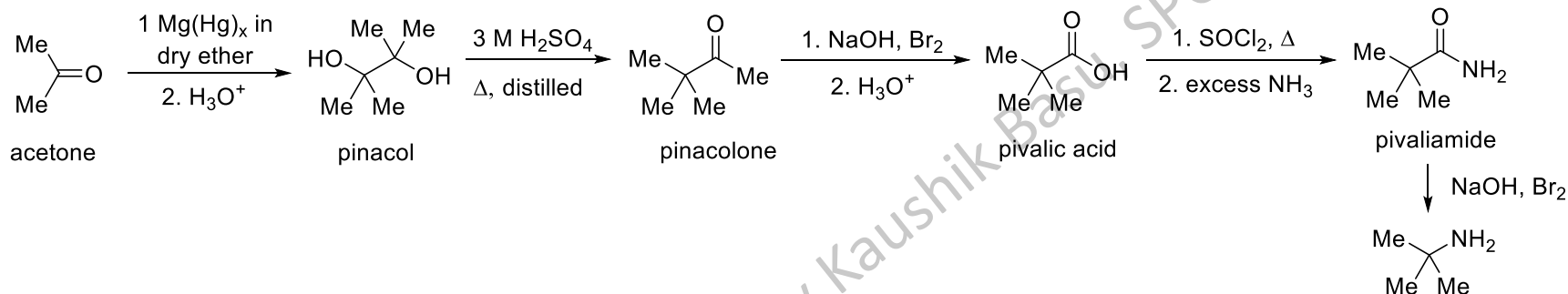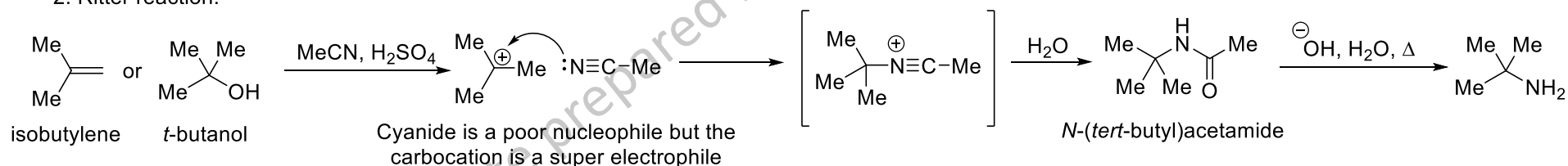

NH$_2$OH.HCl / NaOAc → 1. LAH, dry ether / 2. H$_2$O or H$_2$, Ni

NH$_2$OH.HCl / NaOAc → 1. LAH, dry ether / 2. H$_2$O → cyclohexylamine

Organonitrogen Chemistry

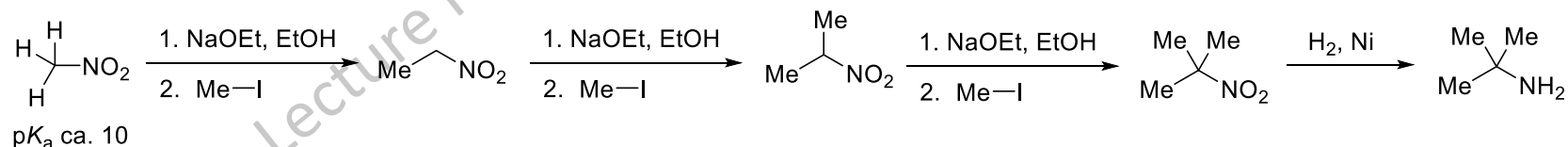Primary amines where N is attached to a tertiary alkyl group: The methods discussed so far will not work.
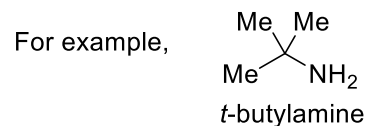
For example,

Me   Me
| |
Me—C—NH$_2$

t-butylamine

1. Recall that compounds containing the *t*-butyl group can be accessed via the Pinacol-Pinacolone rearrangement.

acetone → pinacol → pinacolone → pivalic acid → pivaliamide

2. Ritter reaction:

isobutylene   *t*-butanol

Cyanide is a poor nucleophile but the carbocation is a super electrophile

N-(*tert*-butyl)acetamide

3. Exploiting the acidity of nitromethane:

pK_a ca. 10

We can access

R$_2$R$_3$
|
R$_1$—C—NH$_2$

from

R$_2$R$_3$
|
R$_1$—C—NO$_2$

which, in turn, can be made from H$_3$C—NO$_2$ by sequential alkylations and a final reduction.

R$_1$, R$_2$ and R$_3$ must, however, be amenable to S$_N$2.

Organonitrogen Chemistry

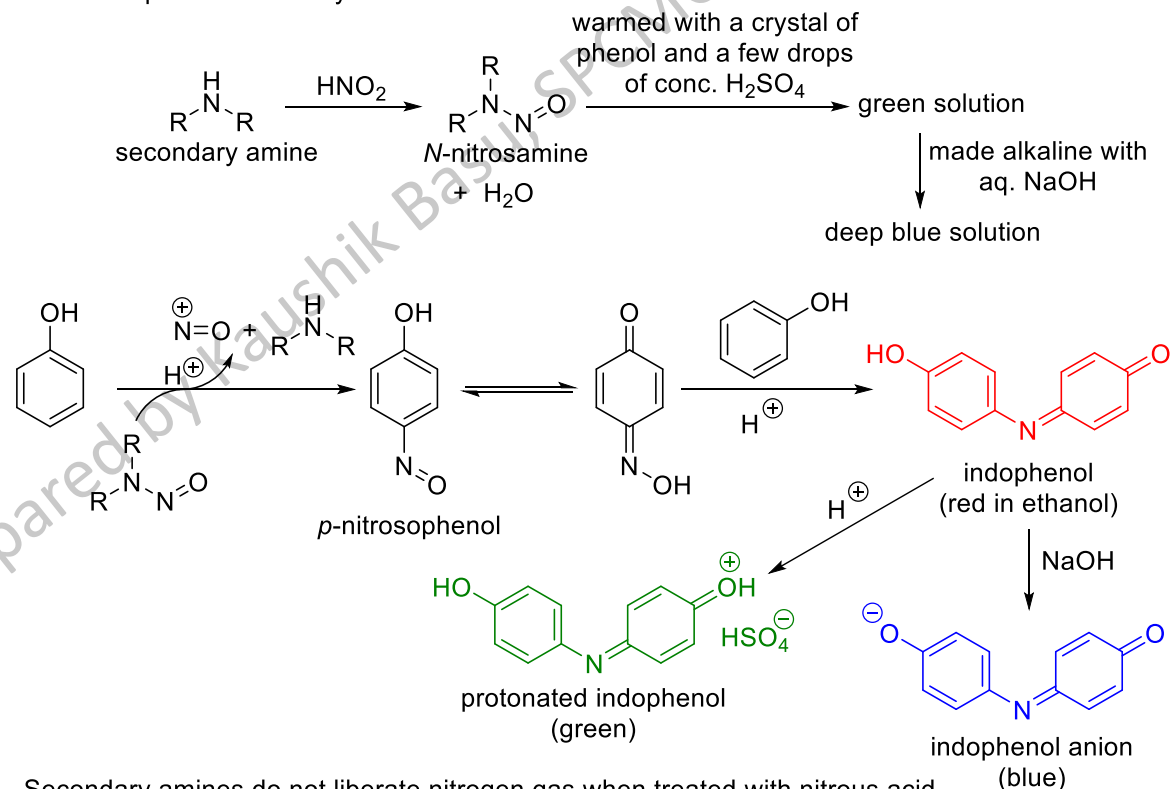Identification and distinction between the three classes of amines: Reaction with nitrous acid

A] Primary amines:

Diazotization with concomitant loss of nitrogen gas (effervescence) leading to a horde of products such as alcohols, amines or olefins.

primary carbocation

redraw

[1,2]-H shift
Wagner-Meerwein rearrangement

secondary carbocation

(S$_N$1) (E1) (S$_N$1)
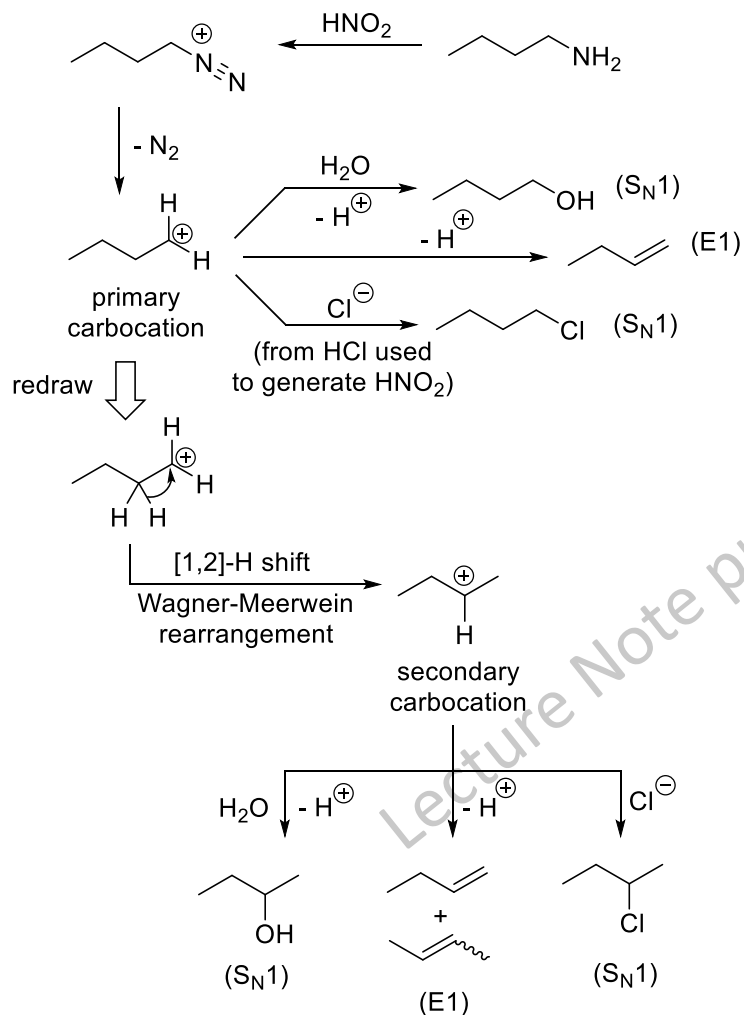
B] Secondary amines:

Secondary amines react with nitrous acid to form *N*-nitrosamines which have oil-like appearance and are steam-volatile. This, on Liebermann's nitroso test responds favourably.

secondary amine → HNO$_2$ → *N*-nitrosamine + H$_2$O

warmed with a crystal of phenol and a few drops of conc. H$_2$SO$_4$ → green solution

made alkaline with aq. NaOH

deep blue solution

p-nitrosophenol

indophenol (red in ethanol)

protonated indophenol (green)

indophenol anion (blue)

Secondary amines do not liberate nitrogen gas when treated with nitrous acid but forms yellow oil.

C] Tertiary amines:
Upon reacting with nitrous acid, tertiary amines neither liberate any nitrogen gas, nor do they separate any oil. They dissolve in the aqueous reaction medium forming nitrite salts.

tertiary amine → HNO$_2$ → nitrite salts