22.7

Reactions of Amines:

A Review and a Preview

Preparation of Amines

Two questions to answer:

1) How is the C—N bond to be formed?
2) How do we obtain the correct oxidation state of nitrogen (and carbon)?

Methods for C—N Bond Formation

Nucleophilic substitution by azide ion (N_3^-) (Section 8.1, 8.13)

Nitration of arenes (Section 12.3)

Nucleophilic ring opening of epoxides by ammonia (Section 16.12)

Nucleophilic addition of amines to aldehydes and ketones (Sections 17.10, 17.11)

Nucleophilic substitution by ammonia on a-halo acids (Section 19.16)

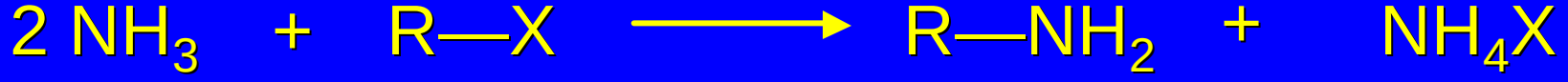
Nucleophilic acyl substitution (Sections 20.3, 20.5, and 20.11)

Hofmann rearrangement (Section 20.17)

22.8
Preparation of Amines by Alkylation of Ammonia

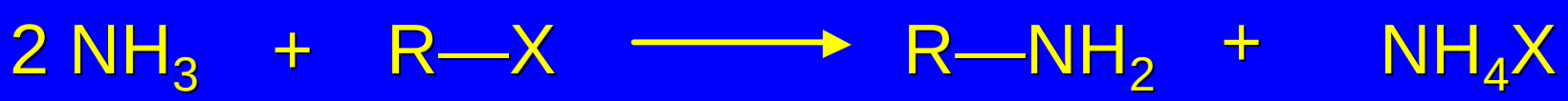
Alkylation of Ammonia

Desired reaction is:

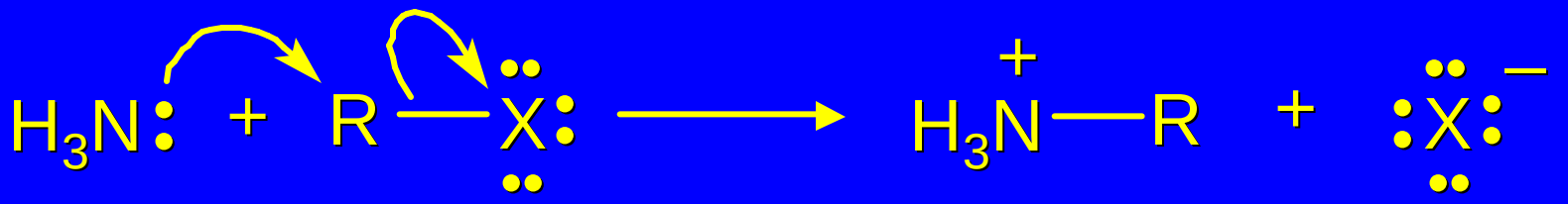


Alkylation of Ammonia

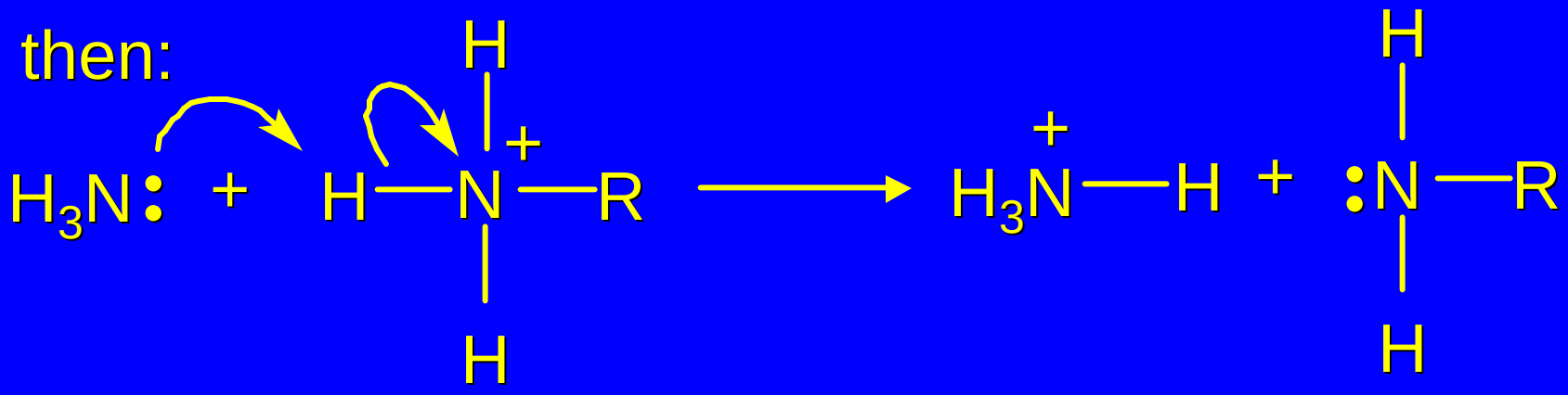
Desired reaction is:



via:

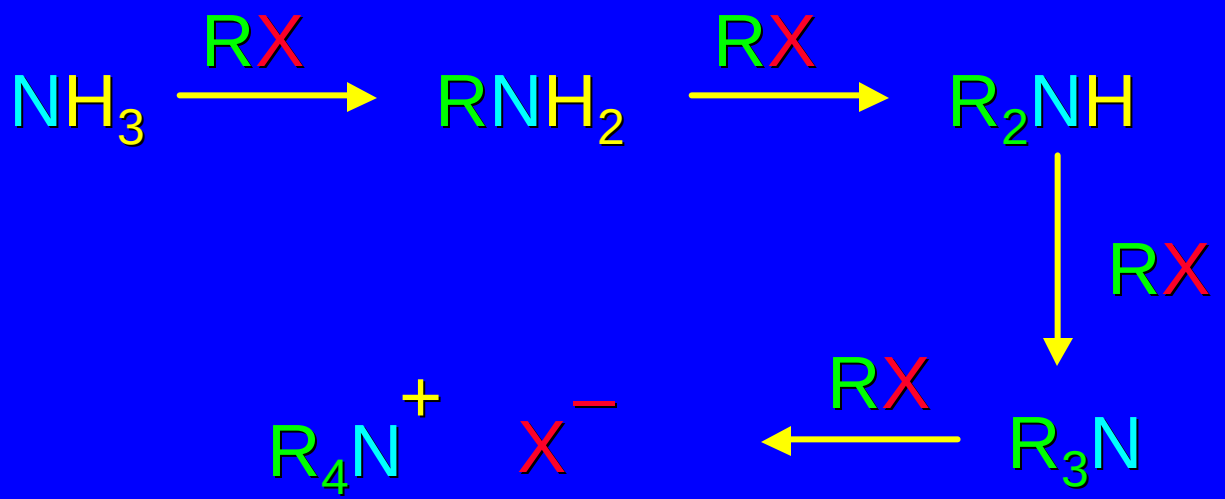


then:

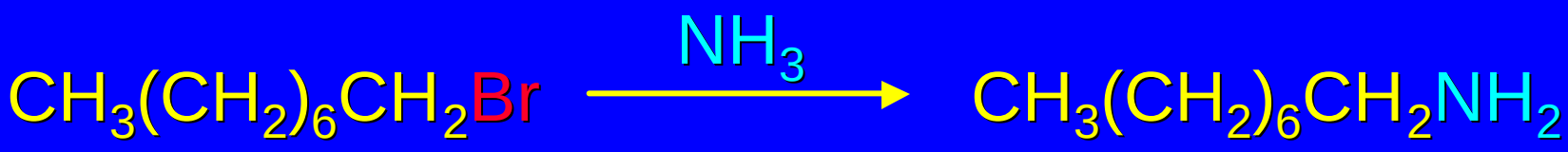


Alkylation of Ammonia

But the method doesn't work well in practice. Usually gives a mixture of primary, secondary, and tertiary amines, plus the quaternary salt.

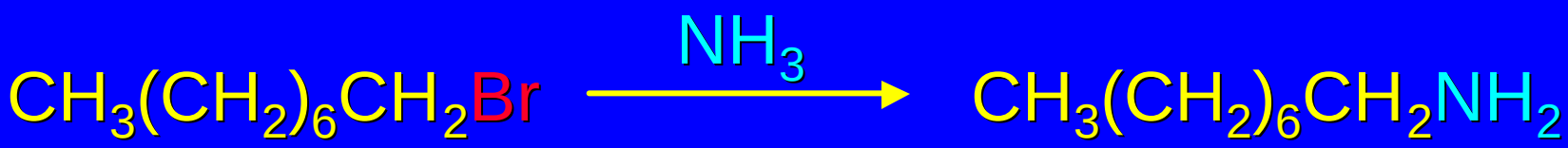


Example



As octylamine is formed, it competes with ammonia for the remaining 1-bromooctane. Reaction of octylamine with 1-bromooctane gives *N*,*N*-dioctylamine.

Example



(45%)

+

$CH_3(CH_2)_6CH_2NHCH_2(CH_2)_6CH_3$

(43%)

As octylamine is formed, it competes with ammonia for the remaining 1-bromooctane. Reaction of octylamine with 1-bromooctane gives *N*,*N*-dioctylamine.

22.9

The Gabriel Synthesis of Primary Alkylamines

Gabriel Synthesis

gives primary amines without formation of secondary, etc. amines as byproducts

uses an S_N2 reaction on an alkyl halide to form the C—N bond

the nitrogen-containing nucleophile
is *N*-potassiophthalimide

Gabriel Synthesis

gives primary amines without formation of secondary, etc. amines as byproducts

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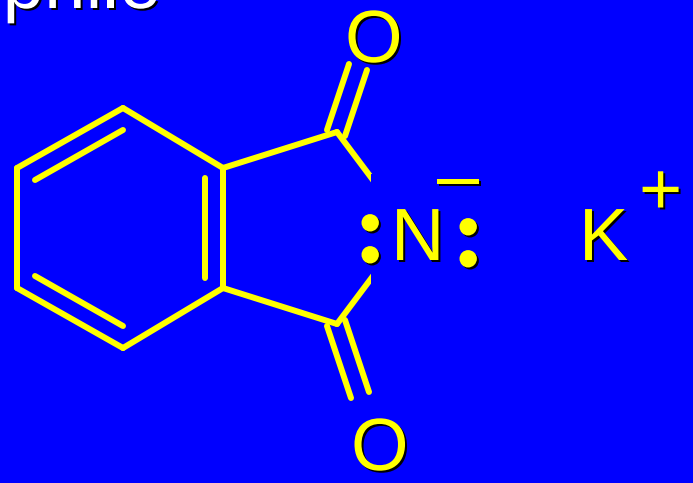
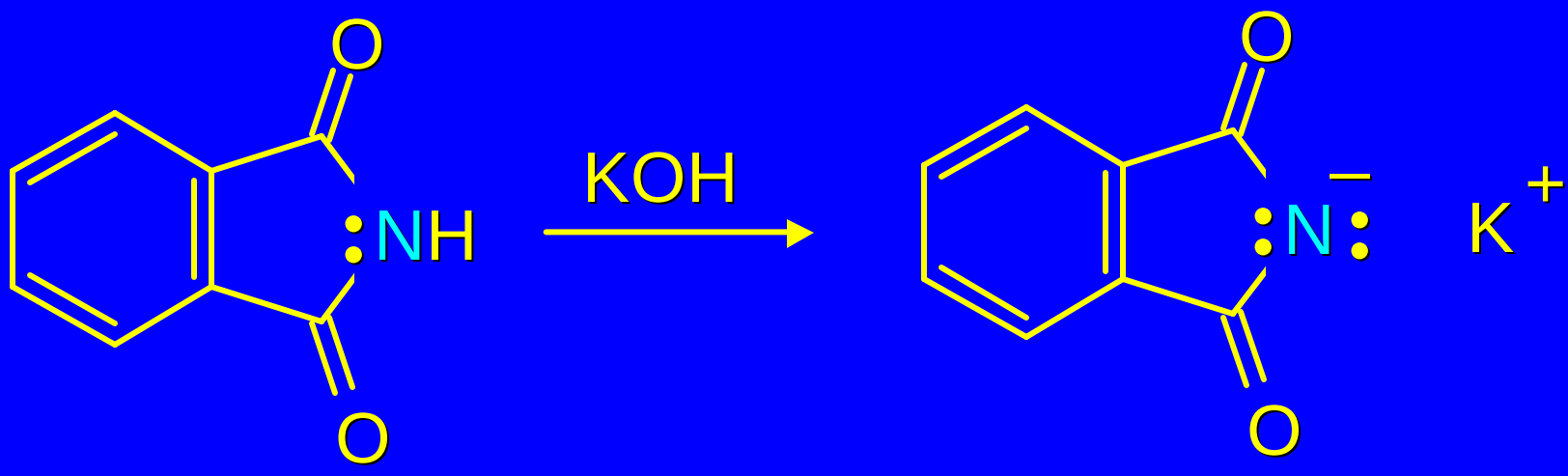


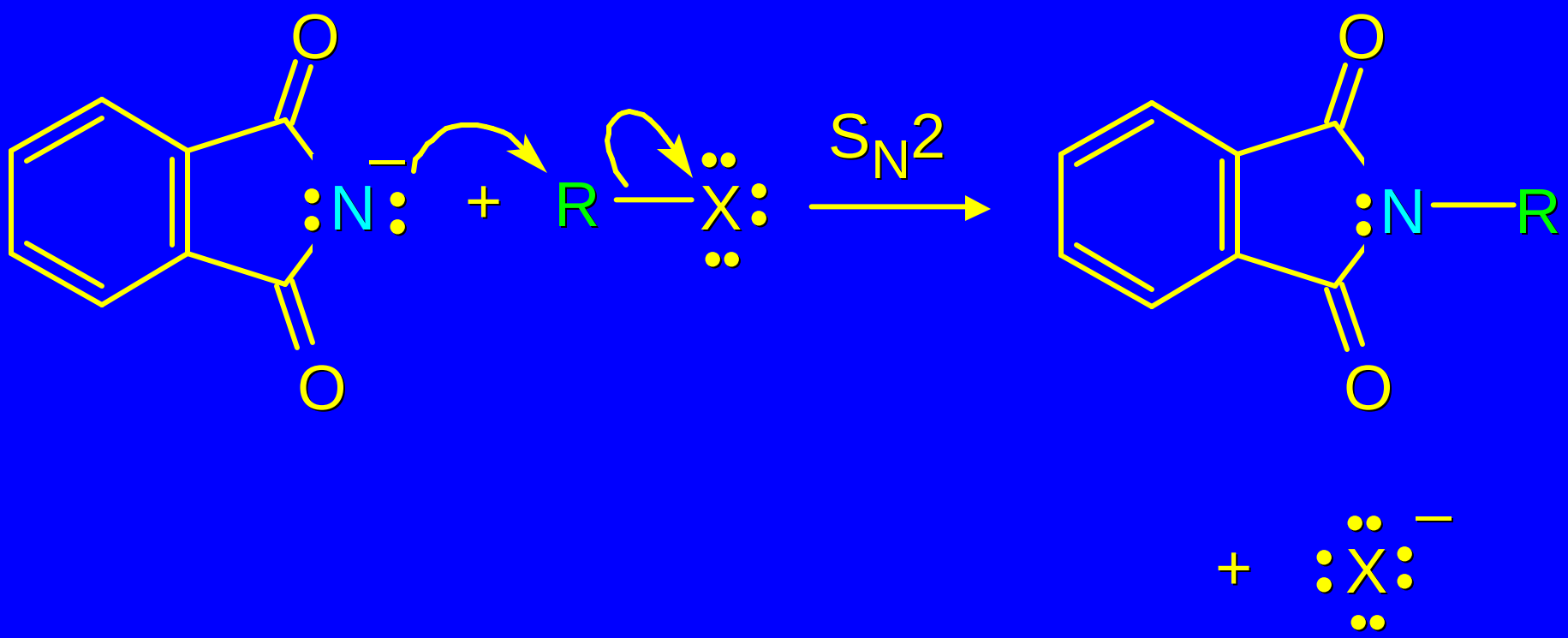
N-Potassiophthalimide

the p*K*a of phthalimide is 8.3

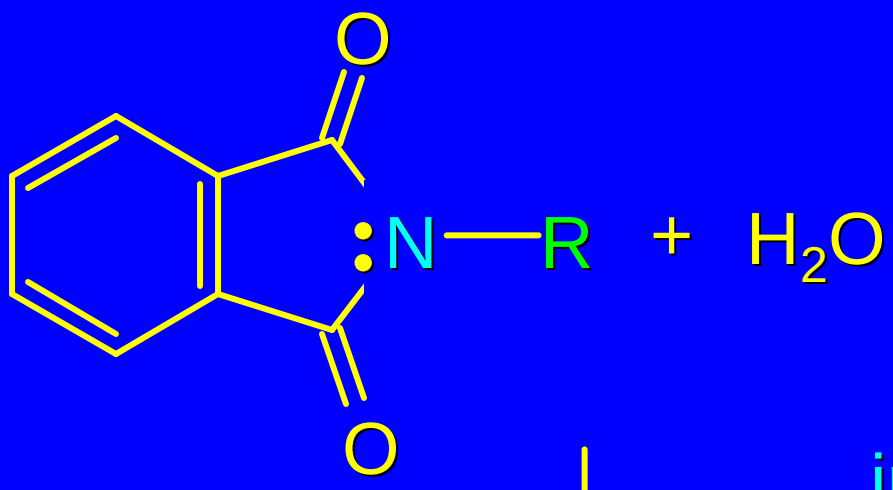
N-potassiophthalimide is easily prepared by the reaction of phthalimide with KOH



N-Potassiophthalimide as a nucleophile



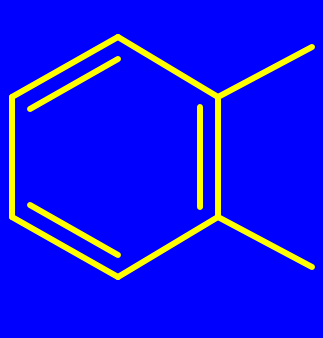
Cleavage of Alkylated Phthalimide



+ H_2O

acid or base

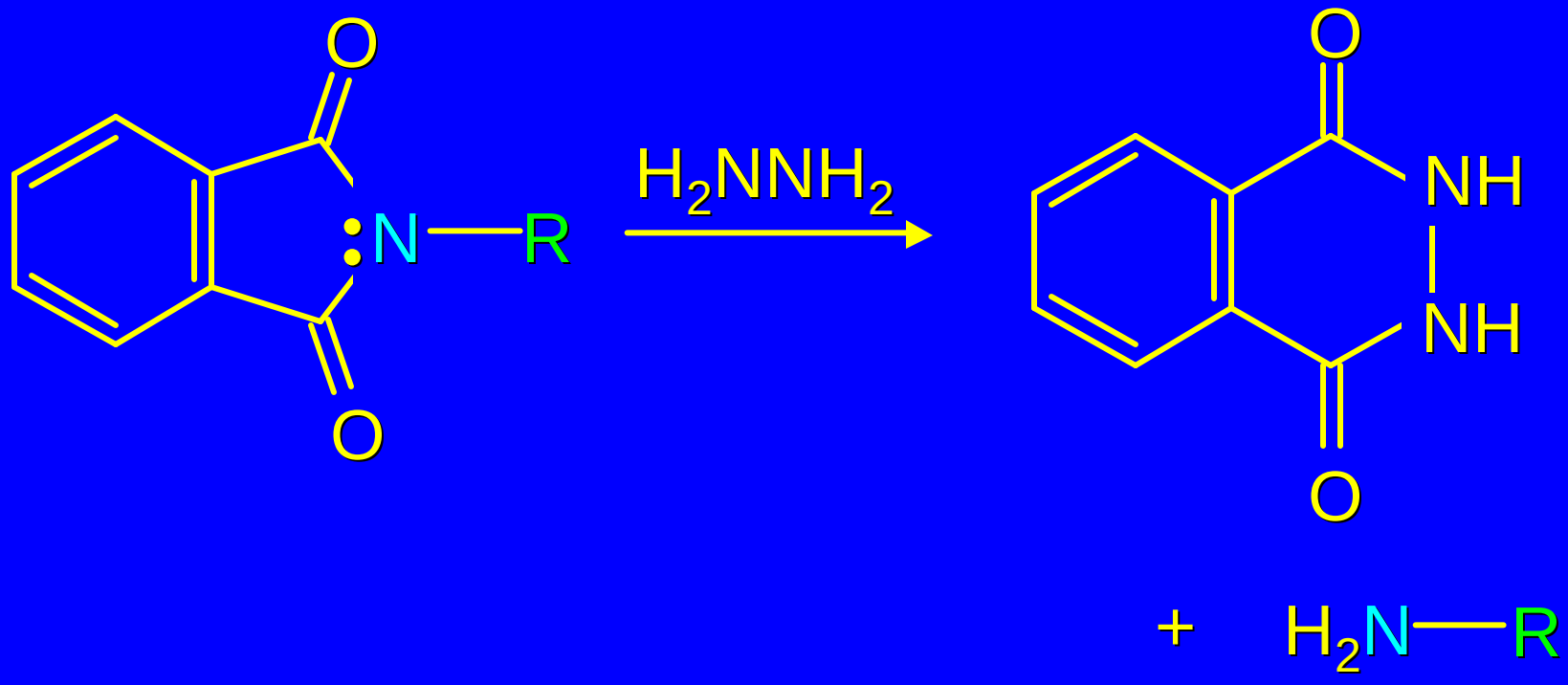
imide hydrolysis is nucleophilic acyl substitution



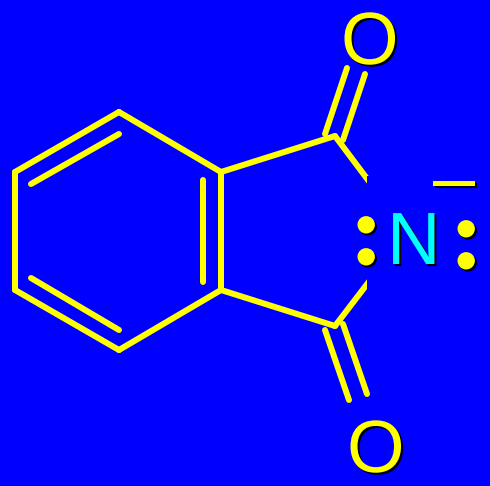
+ H_2N—R

Cleavage of Alkylated Phthalimide

hydrazinolysis is an alternative method of releasing the amine from its phthalimide derivative



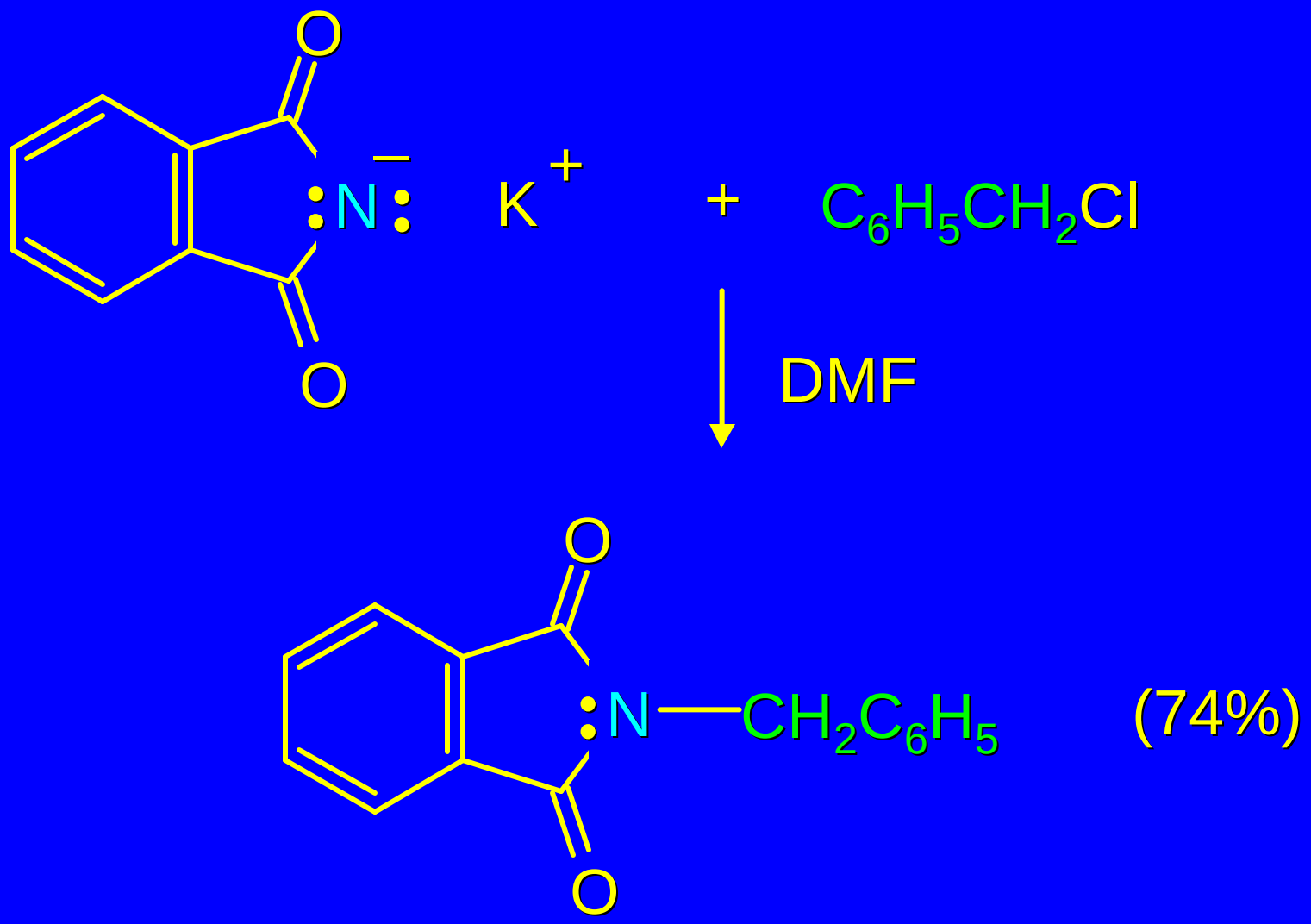
Example



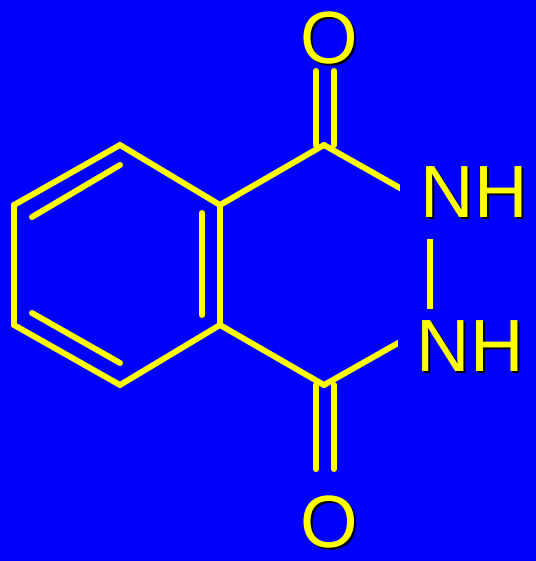
K^+ + $C_6H_5CH_2Cl$

DMF

Example

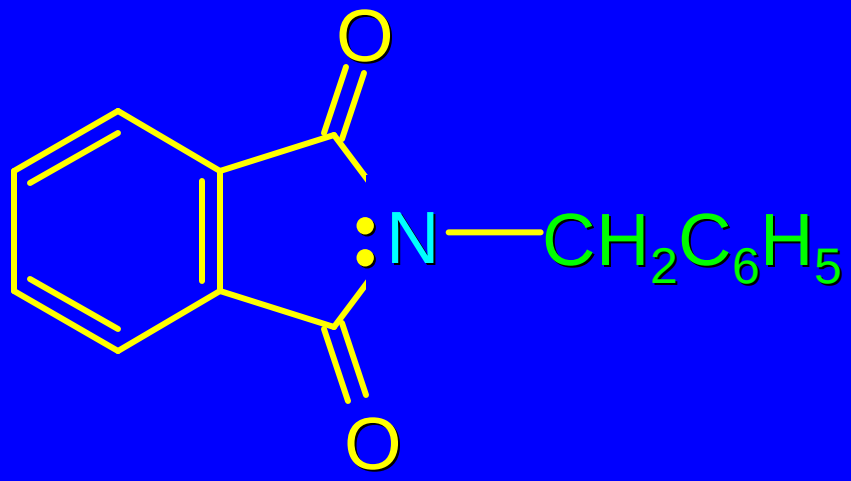


Example



+ $C_6H_5CH_2NH_2$ (97%)

H_2NNH_2



22.10

Preparation of Amines by Reduction

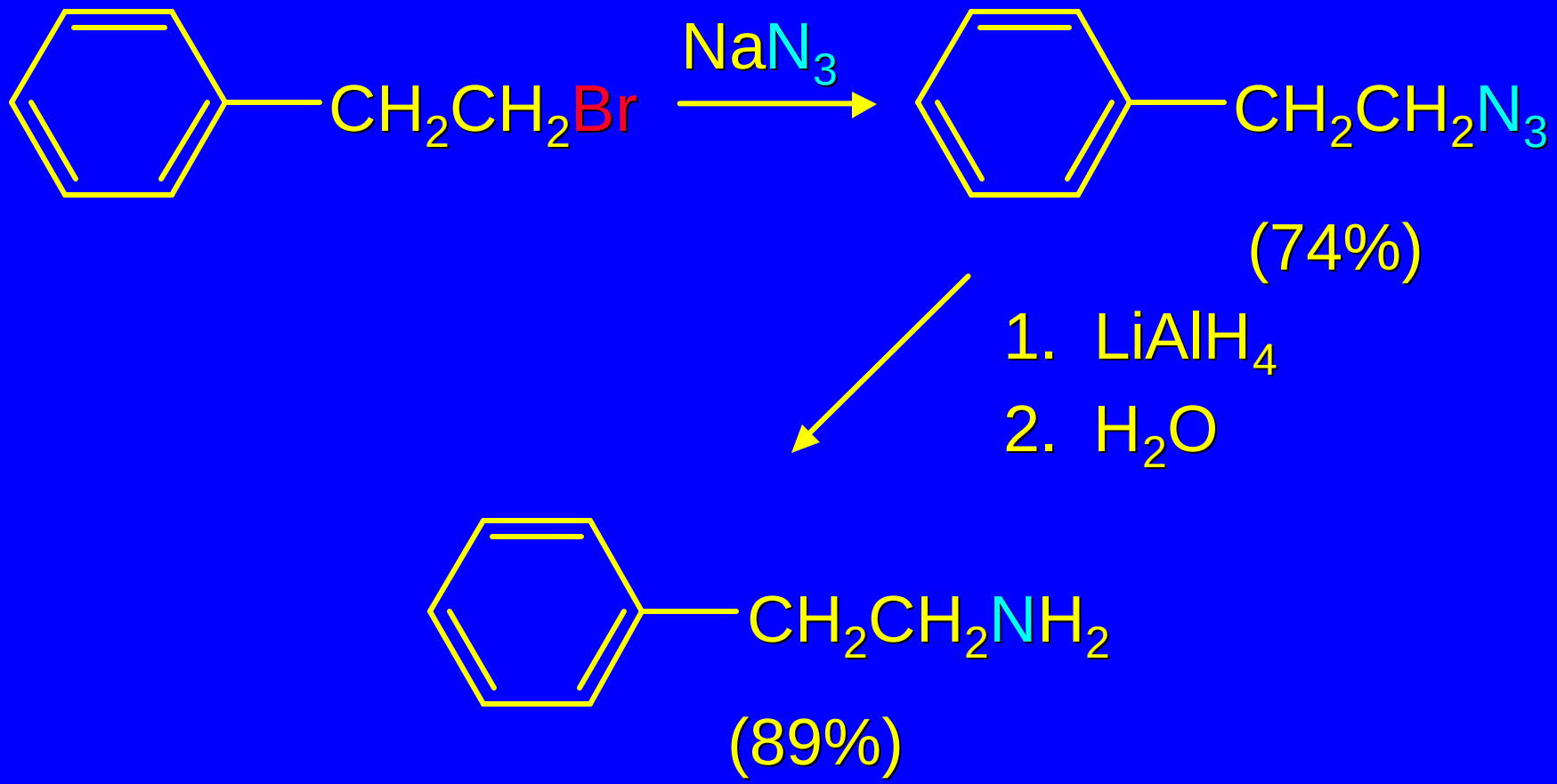
Preparation of Amines by Reduction

almost any nitrogen-containing compound can be reduced to an amine, including:

- azides
- nitriles
- nitro-substituted benzene derivatives
- amides

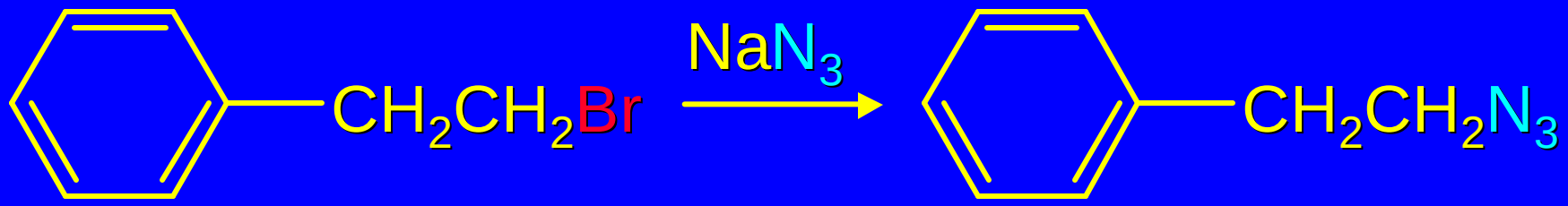
Synthesis of Amines via Azides

S_N2 reaction, followed by reduction, gives a primary alkylamine.



Synthesis of Amines via Azides

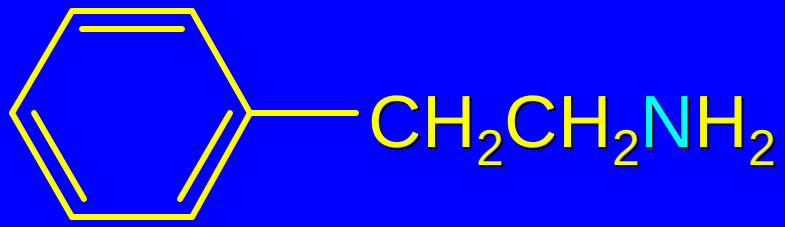
S_N2 reaction, followed by reduction, gives a primary alkylamine.



(74%)

azides may also be reduced by catalytic hydrogenation

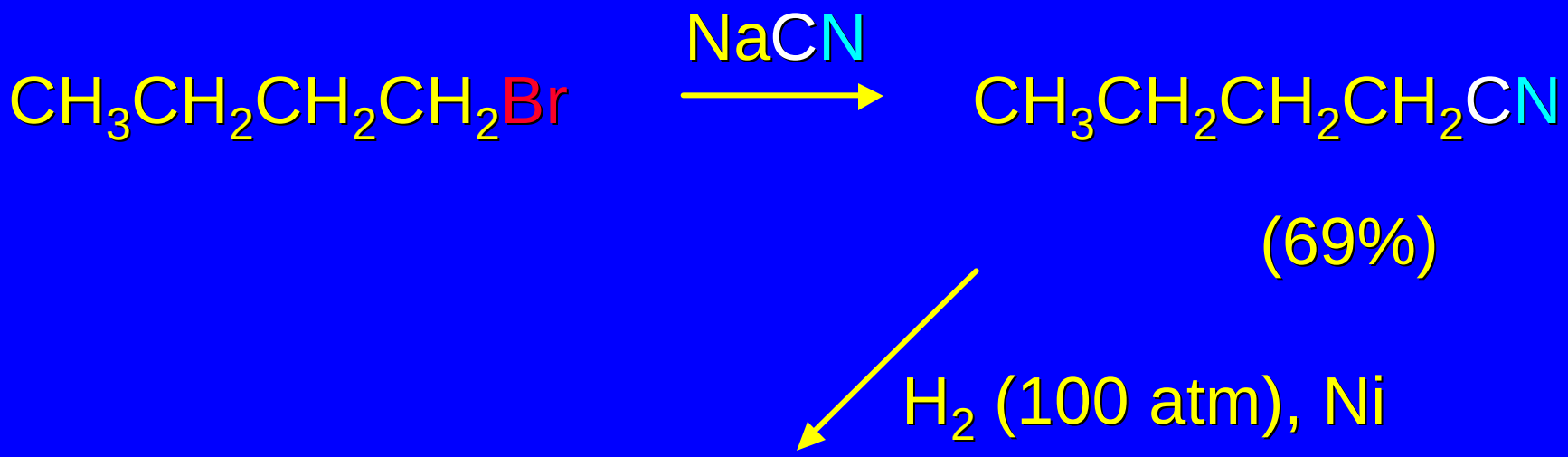
1. $LiAlH_4$
2. H_2O



(89%)

Synthesis of Amines via Nitriles

S_N2 reaction, followed by reduction, gives a primary alkylamine.

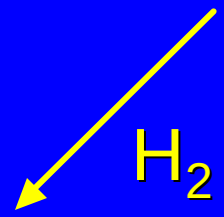


Synthesis of Amines via Nitriles

S_N2 reaction, followed by reduction, gives a primary alkylamine.

(69%)

nitriles may also be reduced by lithium aluminum hydride



$CH_3CH_2CH_2CH_2CH_2NH_2$

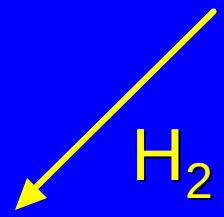
(56%)

Synthesis of Amines via Nitriles

S_N2 reaction, followed by reduction, gives a primary alkylamine.

(69%)

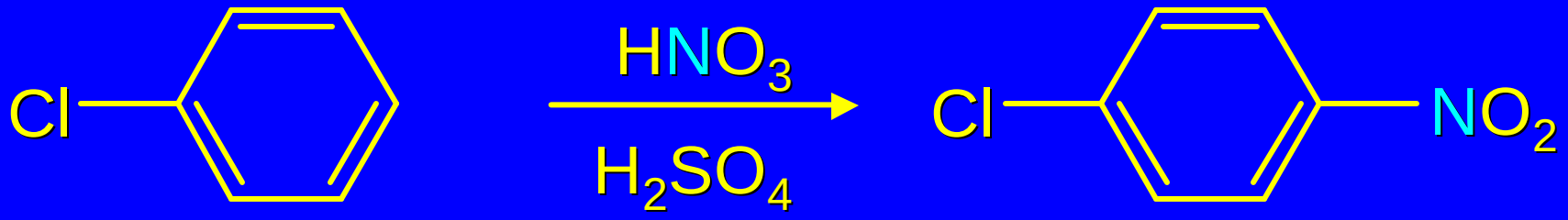
the reduction also works with cyanohydrins



$CH_3CH_2CH_2CH_2CH_2NH_2$

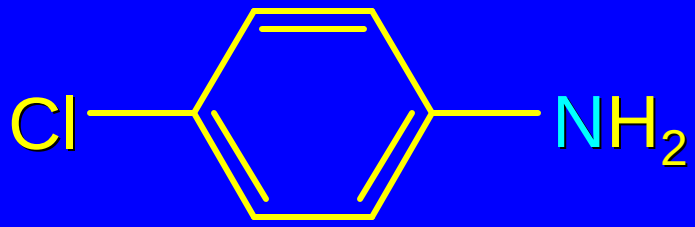
(56%)

Synthesis of Amines via Nitroarenes



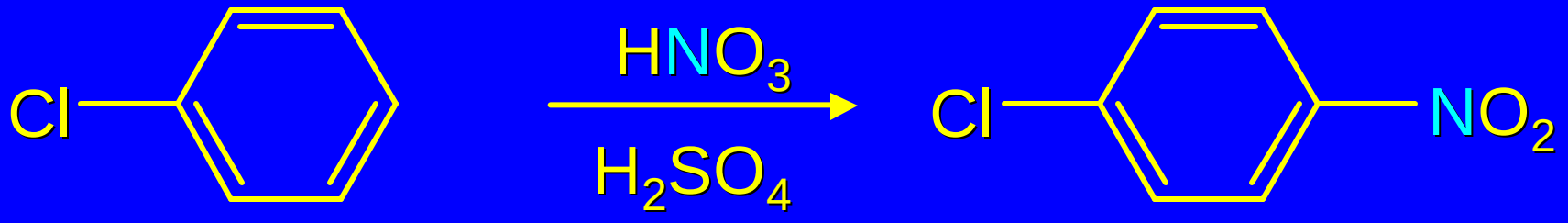
(88-95%)

1. Fe, HCl
2. NaOH



(95%)

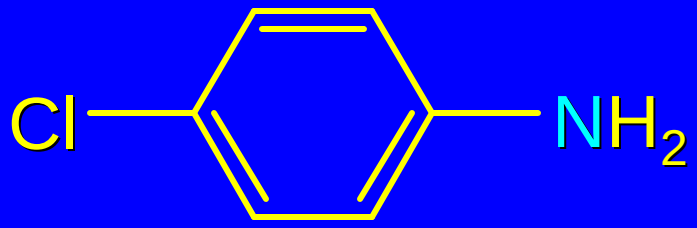
Synthesis of Amines via Nitroarenes



(88-95%)

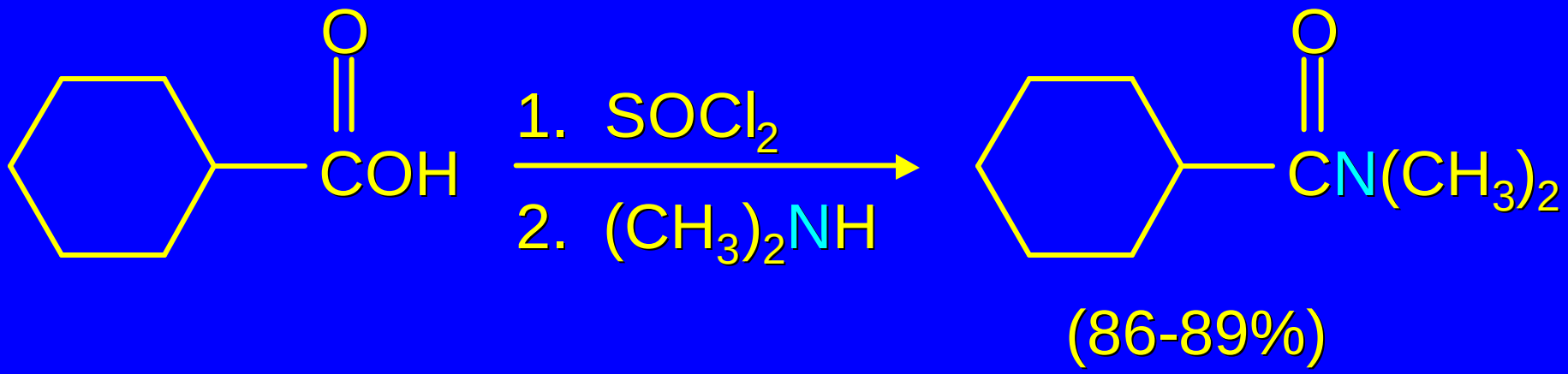
nitro groups may also be reduced with tin (Sn) + HCl or by catalytic hydrogenation

1. Fe, HCl
2. NaOH

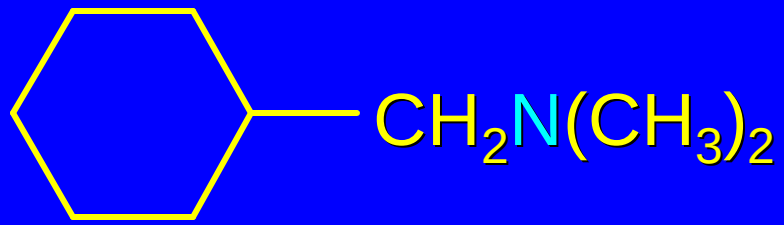


(95%)

Synthesis of Amines via Amides

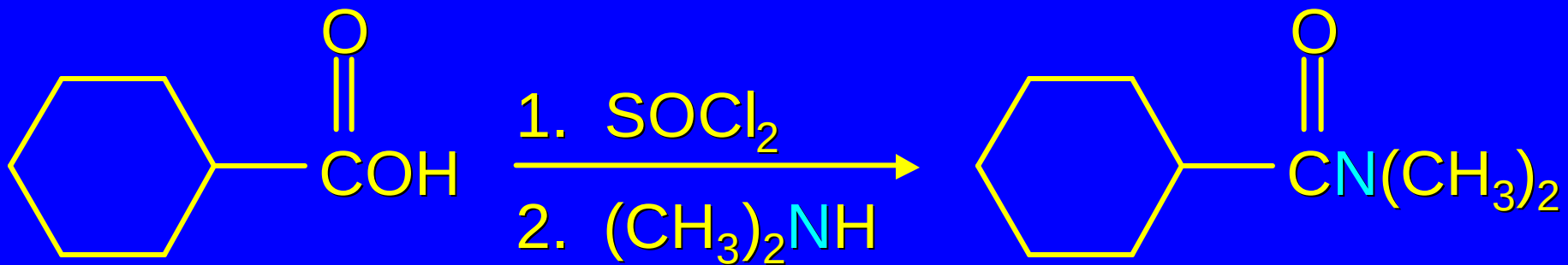


(86-89%)



(88%)

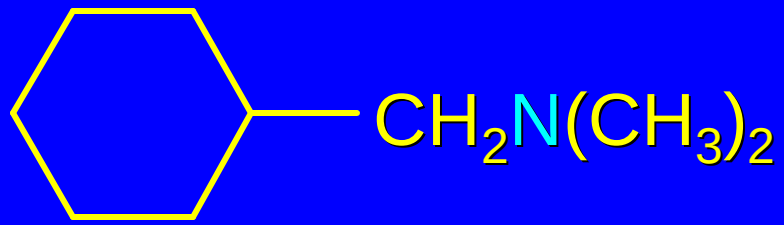
Synthesis of Amines via Amides



(86-89%)

only $LiAlH_4$ is an appropriate reducing agent for this reaction

1. $LiAlH_4$
2. H_2O



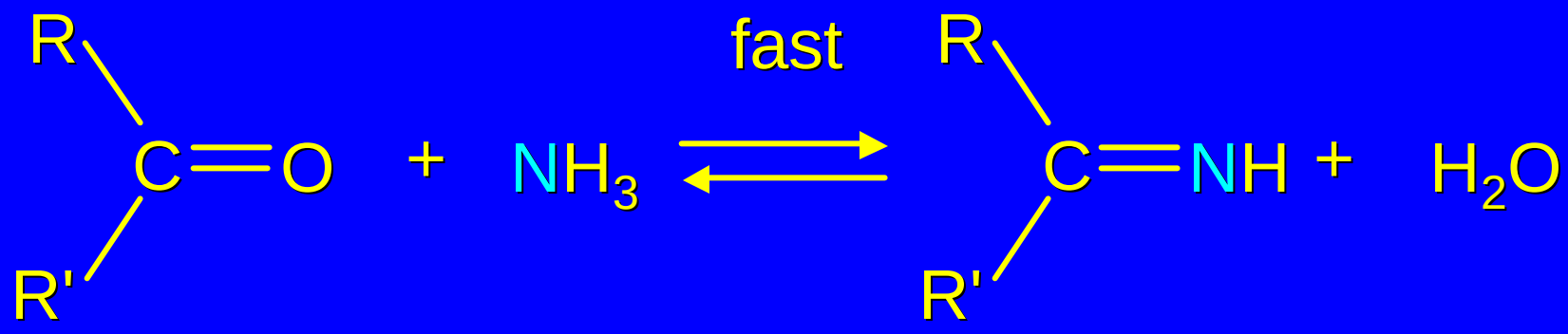
(88%)

22.11

Reductive Amination

Synthesis of Amines via Reductive Amination

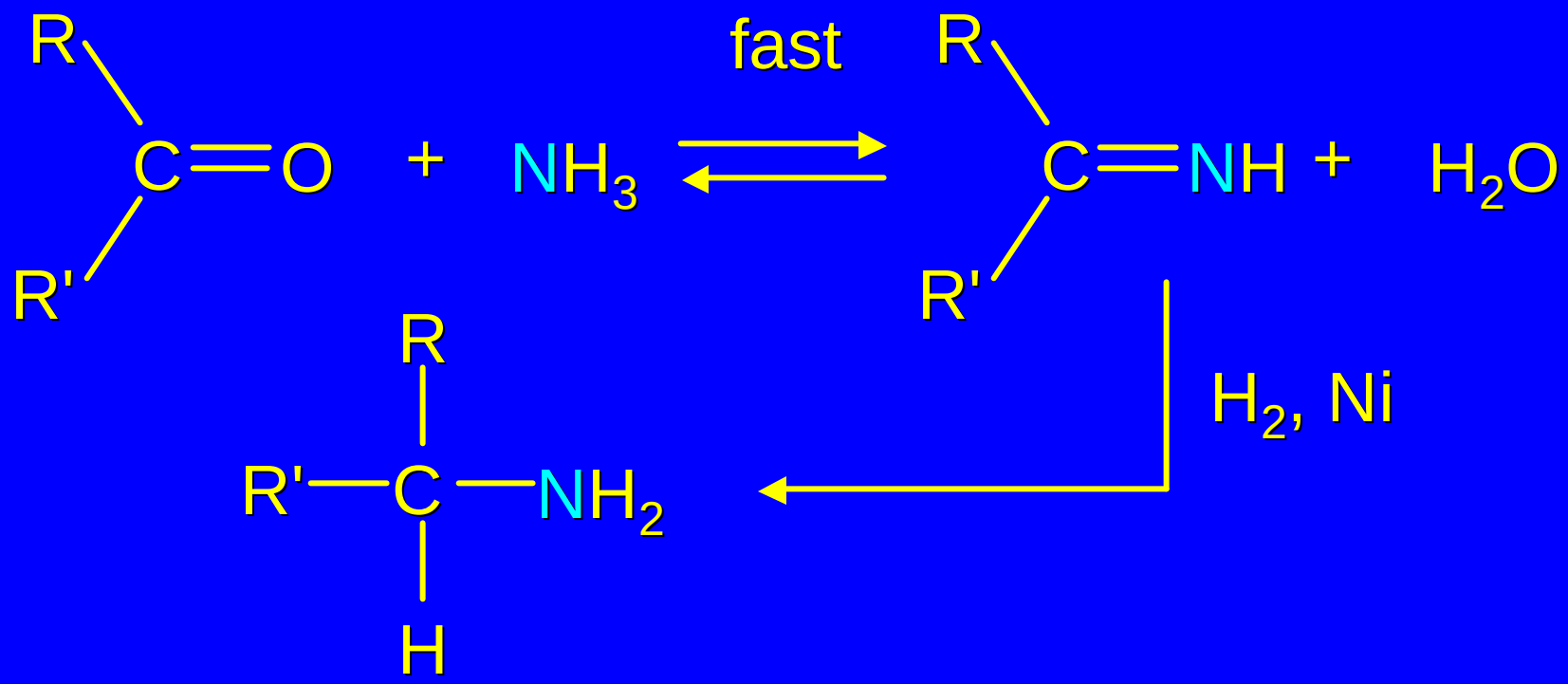
In reductive amination, an aldehyde or ketone is subjected to catalytic hydrogenation in the presence of ammonia or an amine.



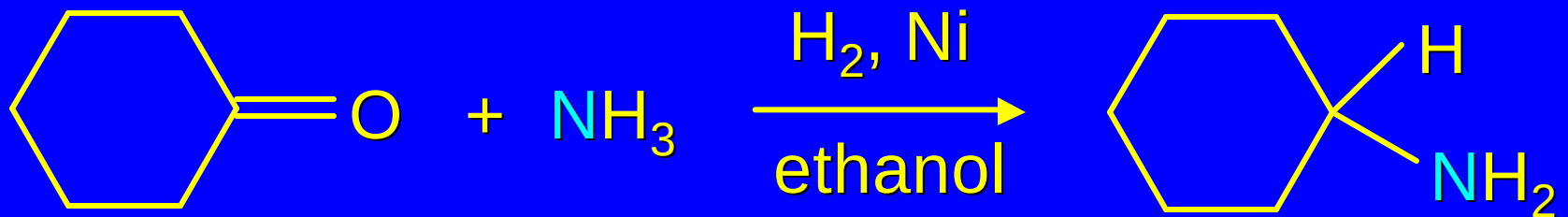
The aldehyde or ketone equilibrates with the imine faster than hydrogenation occurs.

Synthesis of Amines via Reductive Amination

The imine undergoes hydrogenation faster than the aldehyde or ketone. An amine is the product.

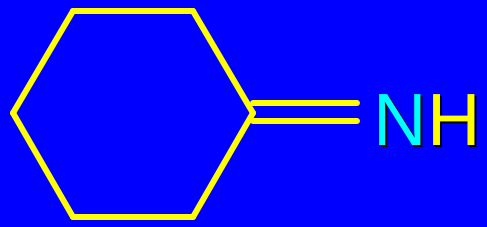


Example: Ammonia gives a primary amine.

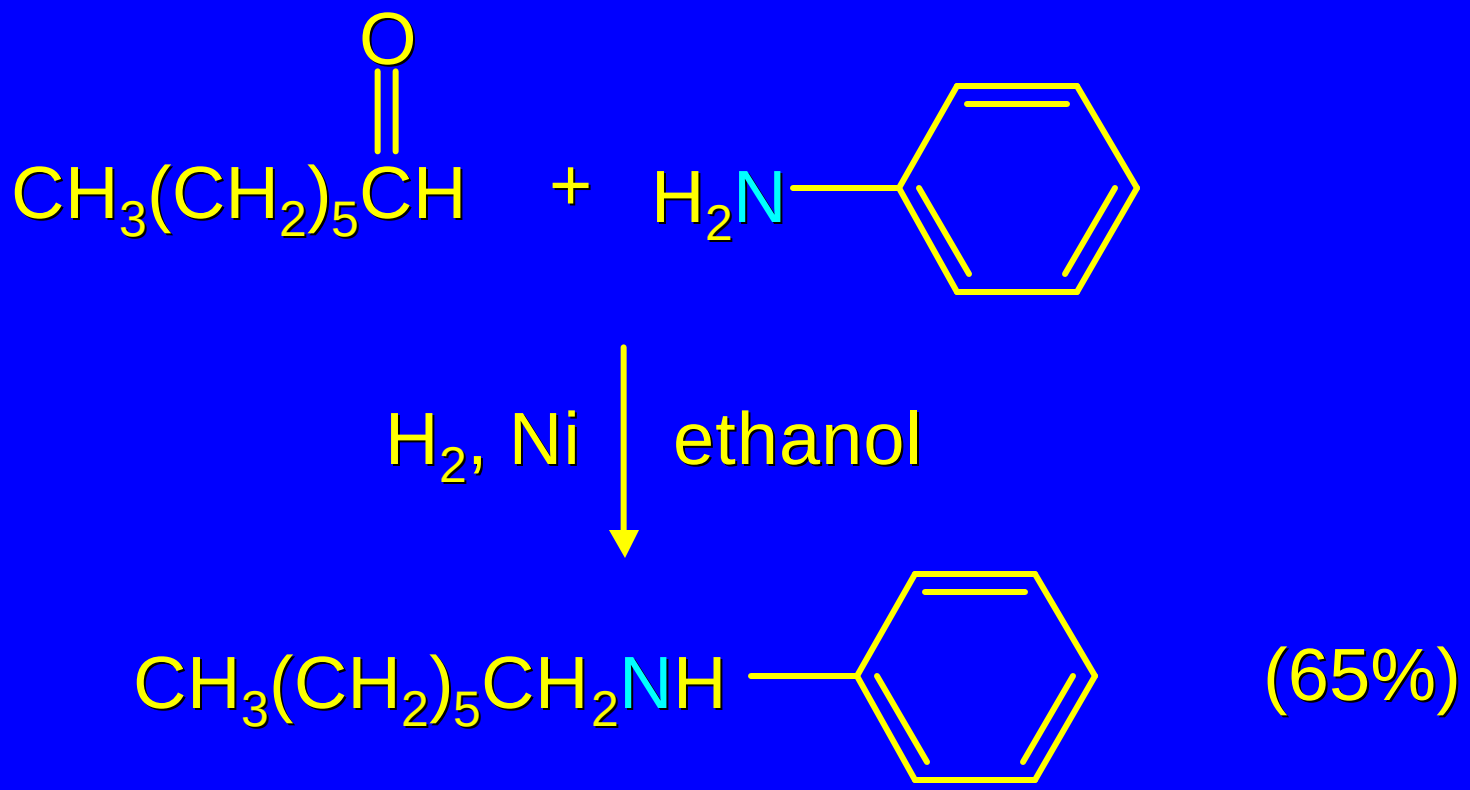


(80%)

via:

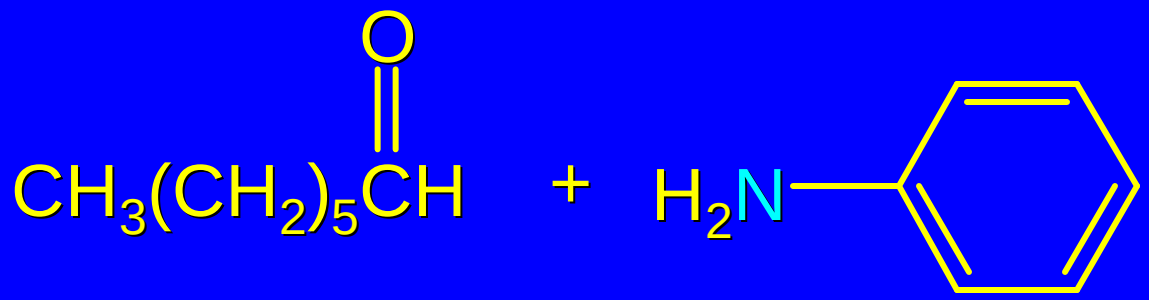


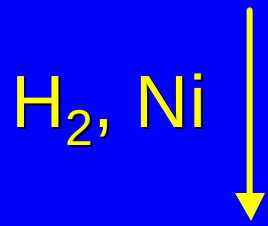
Example: Primary amines give secondary amines

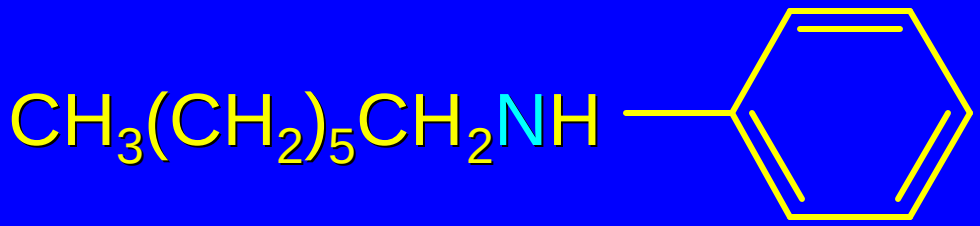


(65%)

Example: Primary amines give secondary amines



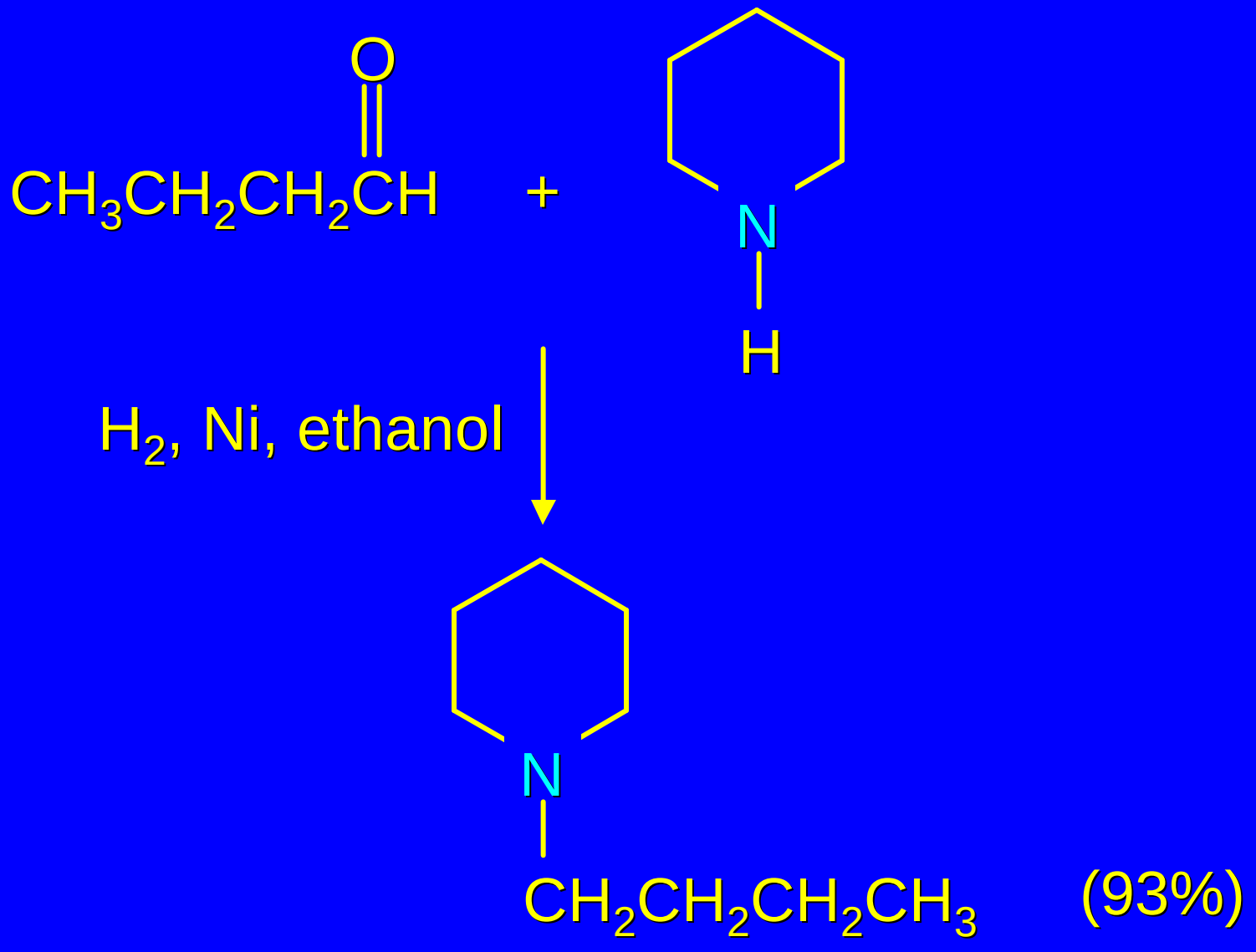




(65%)

via:

Example: Secondary amines give tertiary amines



Example: Secondary amines give tertiary amines

possible intermediates include: