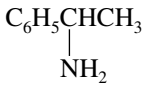
CHAPTER 22

AMINES

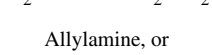
SOLUTIONS TO TEXT PROBLEMS

22.1 (*b*) The amino and phenyl groups are both attached to C-1 of an ethyl group.



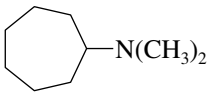
1-Phenylethylamine, or
1-phenylethanamine

(*c*)



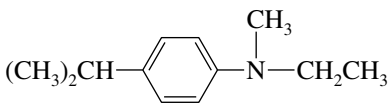
Allylamine, or
2-propen-1-amine

22.2 *N*,*N*-Dimethylcycloheptylamine may also be named as a dimethyl derivative of cycloheptanamine.



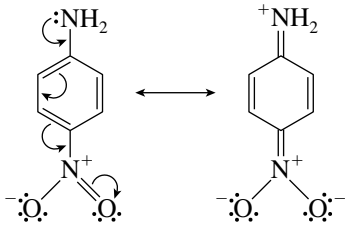
N,*N*-Dimethylcycloheptanamine

22.3 Three substituents are attached to the nitrogen atom; the amine is tertiary. In alphabetical order, the substituents present on the aniline nucleus are ethyl, isopropyl, and methyl. Their positions are specified as *N*-ethyl, 4-isopropyl, and *N*-methyl.



N-Ethyl-4-isopropyl-*N*-methylaniline

22.4 The electron-donating amino group and the electron-withdrawing nitro group are directly conjugated in *p*-nitroaniline. The planar geometry of *p*-nitroaniline suggests that the delocalized resonance form shown is a major contributor to the structure of the compound.



22.5 The pK_b of an amine is related to the equilibrium constant K_b by

$$pK_b = -\log K_b$$

The pK_b of quinine is therefore

$$pK_b = -\log (1 \times 10^{-6}) = 6$$

the values of K_b and pK_b for an amine and K_a and pK_a of its conjugate acid are given by

$$K_a \times K_b = 1 \times 10^{-14}$$

and

$$pK_a + pK_b = 14$$

The values of K_a and pK_a for the conjugate acid of quinine are therefore

$$K_a = \frac{10^{-14}}{K_b} = \frac{1 \times 10^{-14}}{1 \times 10^{-6}} = 1 \times 10^{-8}$$

and

$$pK_a = 14 - pK_b = 14 - 6 = 8$$

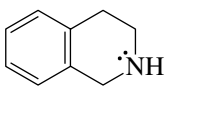
22.6 The Henderson–Hasselbalch equation described in Section 19.4 can be applied to bases such as amines, as well as carboxylic acids. The ratio $[CH_3NH_3^+]/[CH_3NH_2]$ is given by

$$\frac{[CH_3NH_3^+]}{[CH_3NH_2]} = \frac{[H^+]}{K_a}$$

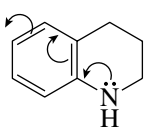
The ionization constant of methylammonium ion is given in the text as 2×10^{-11}. At pH = 7 the hydrogen ion concentration is 1×10^{-7}. Therefore

$$\frac{[CH_3NH_3^+]}{[CH_3NH_2]} = \frac{1 \times 10^{-7}}{2 \times 10^{-11}} = 5 \times 10^3$$

22.7 Nitrogen is attached directly to the aromatic ring in tetrahydroquinoline, making it an arylamine, and the nitrogen lone pair is delocalized into the π system of the aromatic ring. It is less basic than tetrahydroisoquinoline, in which the nitrogen is insulated from the ring by an sp^3-hybridized carbon.



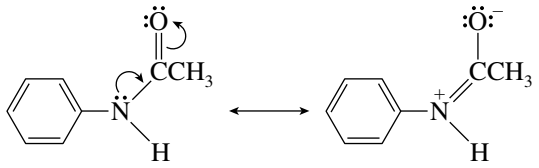
Tetrahydroisoquinoline (an alkylamine): more basic, K_b 2.5×10^{-5} (pK_b 4.6)



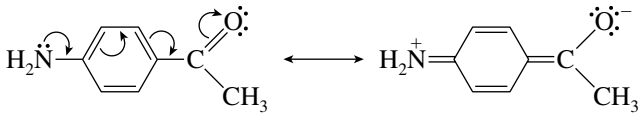
Tetrahydroquinoline (an arylamine): less basic, K_b 1.0×10^{-9} (pK_b 9.0)

See *Learning By Modeling* for the calculated charges on nitrogen.

22.8 (*b*) An acetyl group attached directly to nitrogen as in acetanilide delocalizes the nitrogen lone pair into the carbonyl group. Amides are weaker bases than amines.



(*c*) An acetyl group in a position para to an amine function is conjugated to it and delocalizes the nitrogen lone pair.



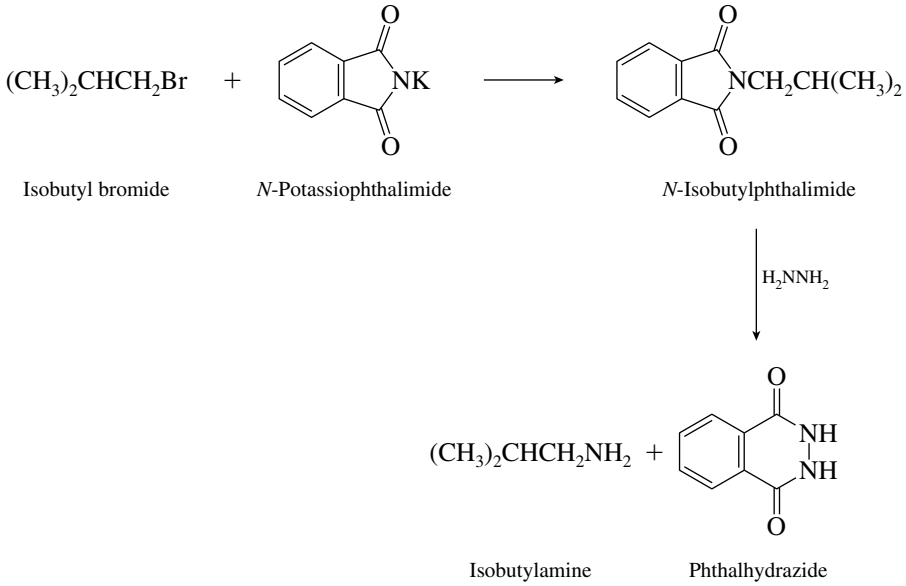
22.9 The reaction that leads to allylamine is nucleophilic substitution by ammonia on allyl chloride.

$$\underset{\text{Allyl chloride}}{H_2C{=}CHCH_2Cl} + \underset{\text{Ammonia}}{2NH_3} \longrightarrow \underset{\text{Allylamine}}{H_2C{=}CHCH_2NH_2} + \underset{\text{Ammonium chloride}}{NH_4Cl}$$

Allyl chloride is prepared by free-radical chlorination of propene (see text page 371).

$$\underset{\text{Propene}}{H_2C{=}CHCH_3} + \underset{\text{Chlorine}}{Cl_2} \xrightarrow{400^\circ C} \underset{\text{Allyl chloride}}{H_2C{=}CHCH_2Cl} + \underset{\text{Hydrogen chloride}}{HCl}$$

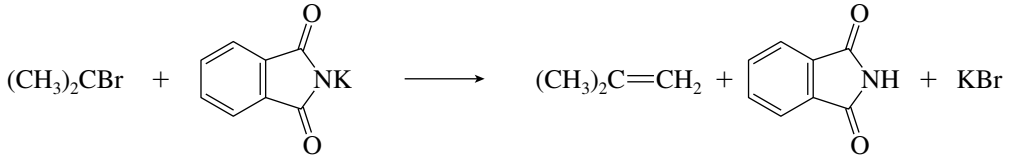
22.10 (*b*) Isobutylamine is $(CH_3)_2CHCH_2NH_2$. It is a primary amine of the type RCH_2NH_2 and can be prepared from a primary alkyl halide by the Gabriel synthesis.



Isobutyl bromide — *N*-Potassiophthalimide — *N*-Isobutylphthalimide

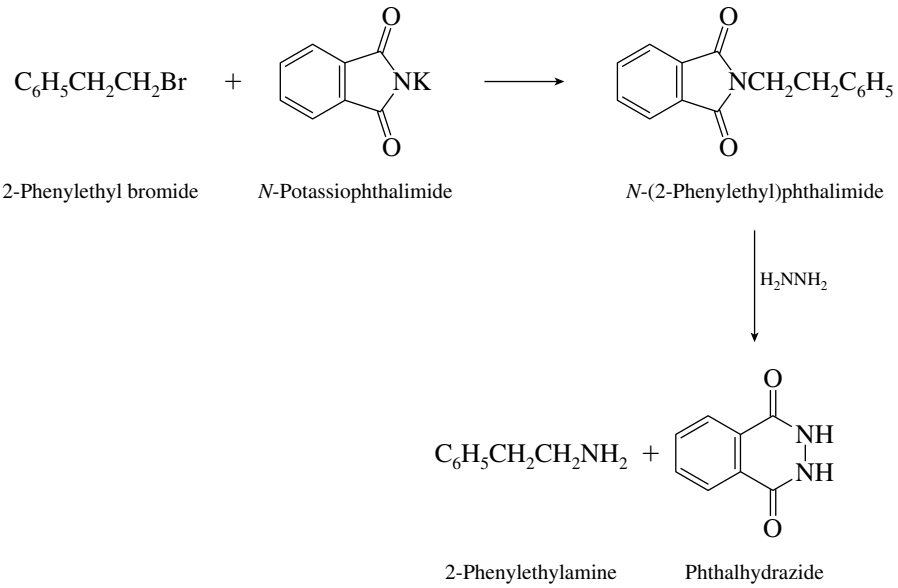
Isobutylamine — Phthalhydrazide

(*c*) Although *tert*-butylamine $(CH_3)_3CNH_2$ is a primary amine, it cannot be prepared by the Gabriel method, because it would require an S_N2 reaction on a tertiary alkyl halide in the first step. Elimination occurs instead.



tert-Butyl bromide — *N*-Potassiophthalimide — 2-Methylpropene — Phthalimide — Potassium bromide

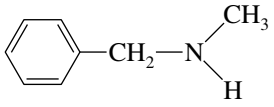
(*d*) The preparation of 2-phenylethylamine by the Gabriel synthesis has been described in the chemical literature.



2-Phenylethyl bromide — *N*-Potassiophthalimide — *N*-(2-Phenylethyl)phthalimide

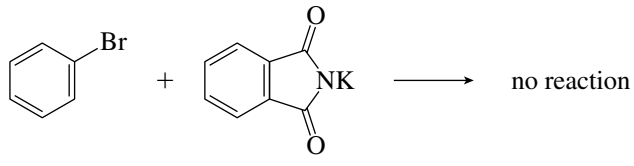
2-Phenylethylamine — Phthalhydrazide

(*e*) The Gabriel synthesis leads to primary amines; *N*-methylbenzylamine is a secondary amine and cannot be prepared by this method.



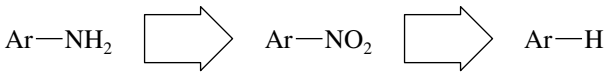
N-Methylbenzylamine
(two carbon substituents on nitrogen; a secondary amine)

(*f*) Aniline cannot be prepared by the Gabriel method. Aryl halides do not undergo nucleophilic substitution under these conditions.



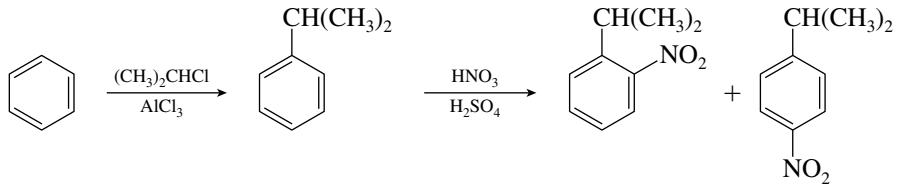
Bromobenzene — *N*-Potassiophthalimide

22.11 For each part of this problem, keep in mind that aromatic amines are derived by reduction of the corresponding aromatic nitro compound. Each synthesis should be approached from the standpoint of how best to prepare the necessary nitroaromatic compound.



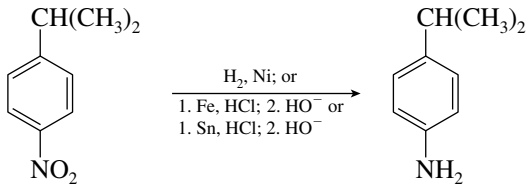
(Ar = substituted aromatic ring)

(*b*) The para isomer of isopropylaniline may be prepared by a procedure analogous to that used for its ortho isomer in part (*a*).

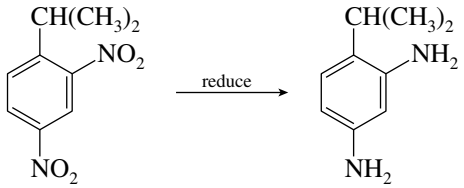


Benzene — Isopropybenzene — *o*-Isopropylnitrobenzene — *p*-Isopropylnitrobenzene

After separating the ortho, para mixture by distillation, the nitro group of *p*-isopropylnitrobenzene is reduced to yield the desired *p*-isopropylaniline.



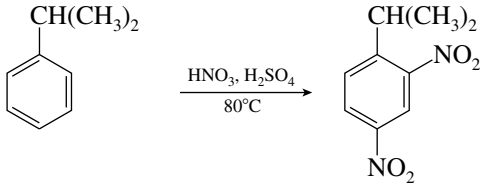
(*c*) The target compound is the reduction product of 1-isopropyl-2,4-dinitrobenzene.



1-Isopropyl-2,4-dinitrobenzene — 4-Isopropyl-1,3-benzenediamine

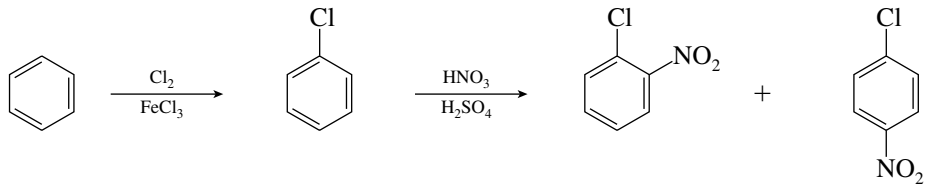
This reduction is carried out in the same way as reduction of an arene that contains only a single nitro group. In this case hydrogenation over a nickel catalyst gave the desired product in 90% yield.

The starting dinitro compound is prepared by nitration of isopropylbenzene.



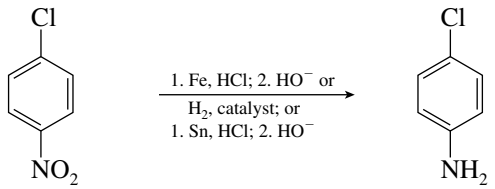
Isopropylbenzene — 1-Isopropyl-2,4-dinitrobenzene (43%)

(*d*) The conversion of *p*-chloronitrobenzene to *p*-chloroaniline was cited as an example in the text to illustrate reduction of aromatic nitro compounds to arylamines. *p*-Chloronitrobenzene is prepared by nitration of chlorobenzene.



Benzene — Chlorobenzene — *o*-Chloronitrobenzene — *p*-Chloronitrobenzene

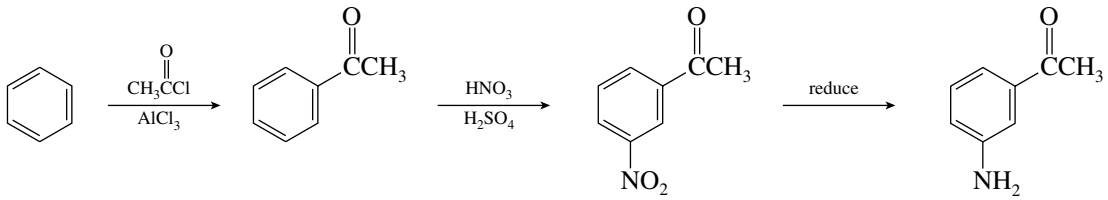
The para isomer accounts for 69% of the product in this reaction (30% is ortho, 1% meta). Separation of *p*-chloronitrobenzene and its reduction completes the synthesis.



p-Chloronitrobenzene — *p*-Chloroaniline

Chlorination of nitrobenzene would not be a suitable route to the required intermediate, because it would produce mainly *m*-chloronitrobenzene.

(*e*) The synthesis of *m*-aminoacetophenone may be carried out by the scheme shown:

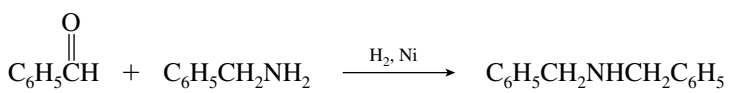


Benzene — Acetophenone — *m*-Nitroacetophenone — *m*-Aminoacetophenone

The acetyl group is attached to the ring by Friedel–Crafts acylation. It is a meta director, and its nitration gives the proper orientation of substituents. The order of the first two steps cannot be reversed, because Friedel–Crafts acylation of nitrobenzene is not possible (Section 12.16). Once prepared, *m*-nitroacetophenone can be reduced to *m*-nitroaniline by any of a number of reagents. Indeed, all three reducing combinations described in the text have been employed for this transformation.

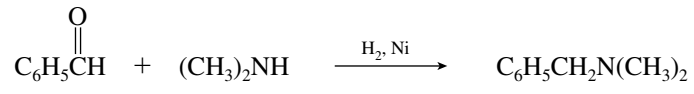
	Reducing agent	Yield (%)
m-Nitroacetophenone	H_2, Pt	94
↓	Fe, HCl	84
m-Aminoacetophenone	Sn, HCl	82

22.12 (*b*) Dibenzylamine is a secondary amine and can be prepared by reductive amination of benzaldehyde with benzylamine.



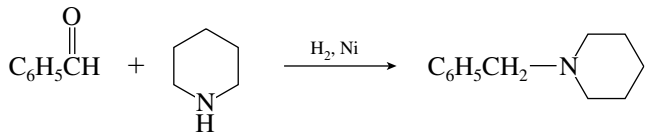
Benzaldehyde — Benzylamine — Dibenzylamine

(*c*) *N*,*N*-Dimethylbenzylamine is a tertiary amine. Its preparation from benzaldehyde requires dimethylamine, a secondary amine.



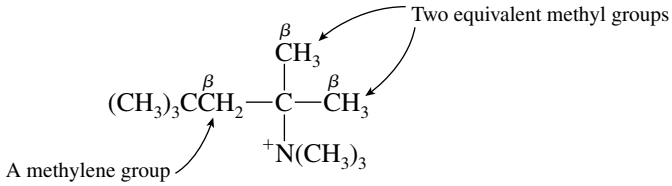
Benzaldehyde Dimethylamine *N*,*N*-Dimethylbenzylamine

(*d*) The preparation of *N*-butylpiperidine by reductive amination is described in the text in Section 22.11. An analogous procedure is used to prepare *N*-benzylpiperidine.

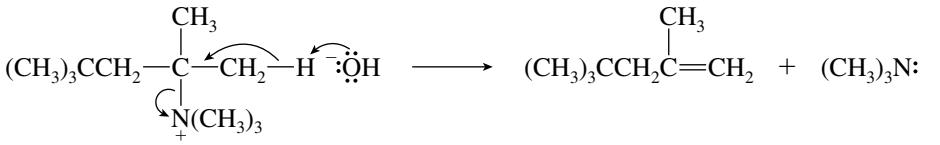


Benzaldehyde Piperidine *N*-Benzylpiperidine

22.13 (*b*) First identify the available β hydrogens. Elimination must involve a proton from the carbon atom adjacent to the one that bears the nitrogen.



It is a proton from one of the methyl groups, rather than one from the more sterically hindered methylene, that is lost on elimination.

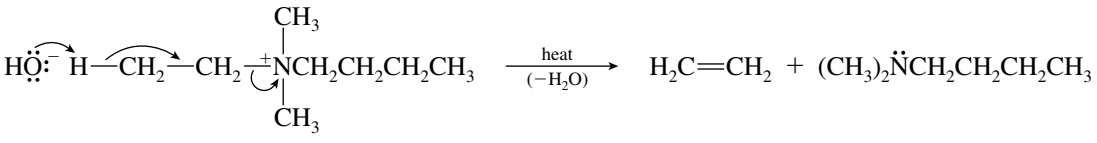


(1,1,3,3-Tetramethylbutyl)-trimethylammonium hydroxide

2,4,4-Trimethyl-1-pentene (only alkene formed, 70% isolated yield)

Trimethylamine

(*c*) The base may abstract a proton from either of two β carbons. Deprotonation of the β methyl carbon yields ethylene.

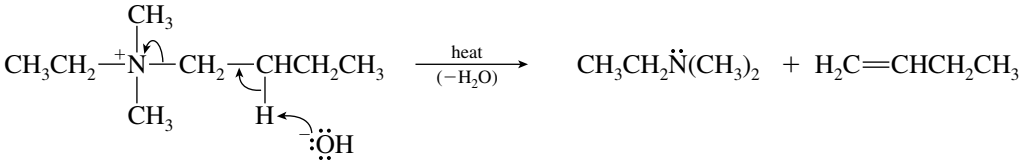


N-Ethyl-*N*,*N*-dimethylbutylammonium hydroxide

Ethylene

N,*N*-Dimethylbutylamine

Deprotonation of the β methylene carbon yields 1-butene.



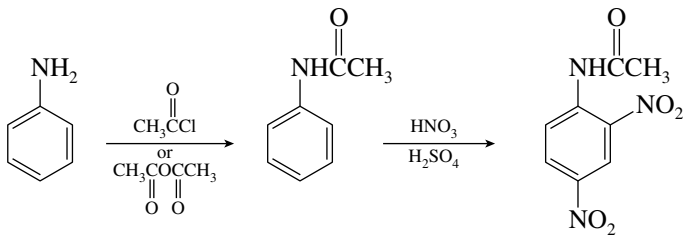
N-Ethyl-*N*,*N*-dimethylbutylammonium hydroxide

N,*N*-Dimethylethylamine

1-Butene

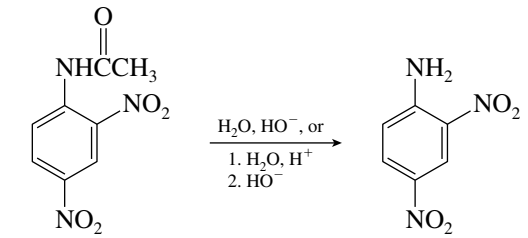
The preferred order of proton removal in Hofmann elimination reactions is β CH_3 > β CH_2 > β CH. Ethylene is the major alkene formed, the observed ratio of ethylene to 1-butene being 98 : 2.

22.14 (*b*) The pattern of substituents in 2,4-dinitroaniline suggests that they can be introduced by dinitration. Since nitration of aniline itself is not practical, the amino group must be protected by conversion to its *N*-acetyl derivative.



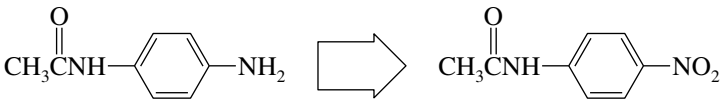
Aniline Acetanilide 2,4-Dinitroacetanilide

Hydrolysis of the amide bond in 2,4-dinitroacetanilide furnishes the desired 2,4-dinitroaniline.



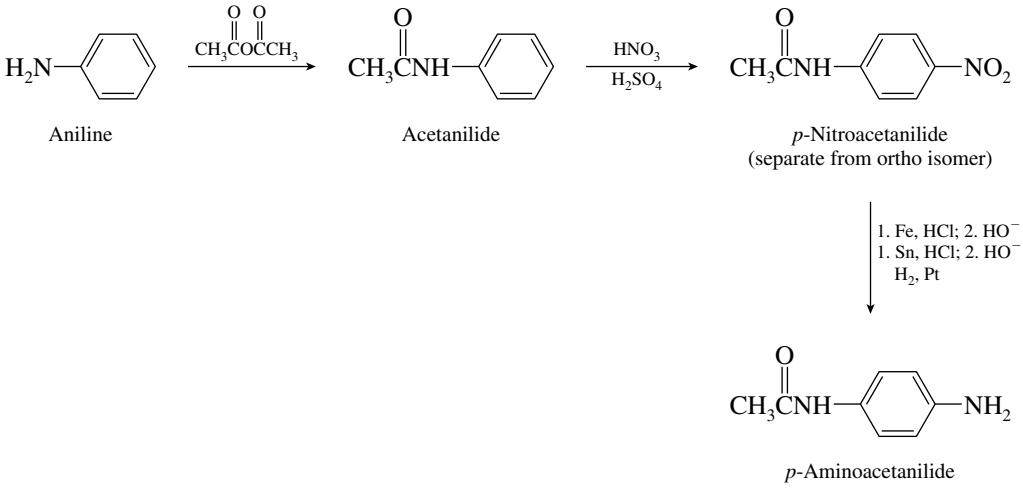
2,4-Dinitroacetanilide 2,4-Dinitroaniline

(*c*) Retrosynthetically, *p*-aminoacetanilide may be derived from *p*-nitroacetanilide.



p-Aminoacetanilide *p*-Nitroacetanilide

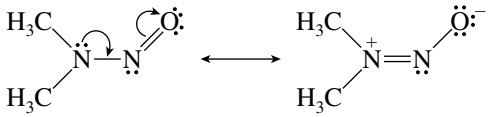
This suggests the sequence



Aniline Acetanilide *p*-Nitroacetanilide (separate from ortho isomer)

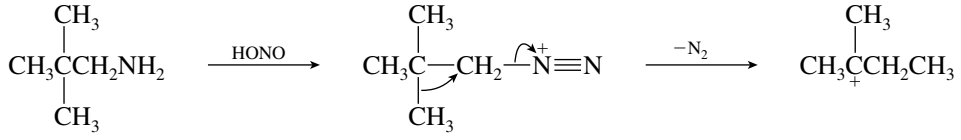
p-Aminoacetanilide

22.15 The principal resonance forms of *N*-nitrosodimethylamine are



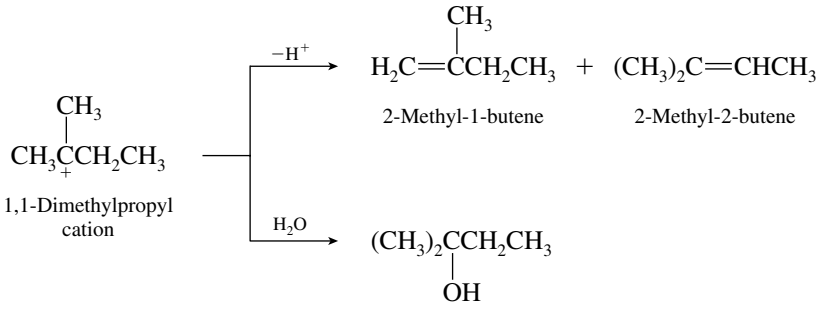
All atoms (except hydrogen) have octets of electrons in each of these structures. Other resonance forms are less stable because they do not have a full complement of electrons around each atom.

22.16 Deamination of 1,1-dimethylpropylamine gives products that result from 1,1-dimethylpropyl cation. Because 2,2-dimethylpropylamine gives the same products, it is likely that 1,1-dimethylpropyl cation is formed from 2,2-dimethylpropylamine by way of its diazonium ion. A carbocation rearrangement is indicated.



2,2-Dimethylpropylamine — 2,2-Dimethylpropyldiazonium ion — 1,1-Dimethylpropyl cation

Once formed, 1,1-dimethylpropyl cation loses a proton to form an alkene or is captured by water to give an alcohol.

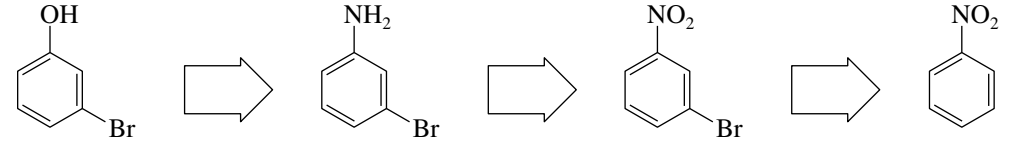


1,1-Dimethylpropyl cation

2-Methyl-1-butene + 2-Methyl-2-butene

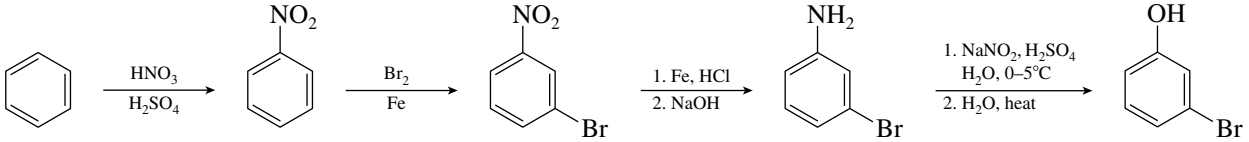
2-Methyl-2-butanol

22.17 Phenols may be prepared by diazotization of the corresponding aniline derivative. The problem simplifies itself, therefore, to the preparation of *m*-bromoaniline. Recognizing that arylamines are ultimately derived from nitroarenes, we derive the retrosynthetic sequence of intermediates:

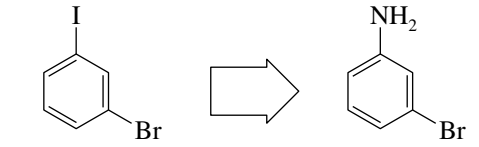


m-Bromophenol — *m*-Bromoaniline — *m*-Bromonitrobenzene — Nitrobenzene

The desired reaction sequence is straightforward, using reactions that were discussed previously in the text.

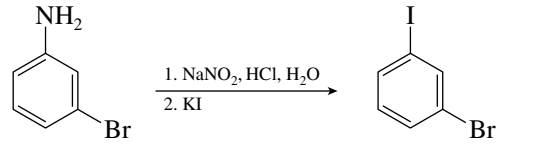


22.18 The key to this problem is to recognize that the iodine substituent in *m*-bromoiodobenzene is derived from an arylamine by diazotization.



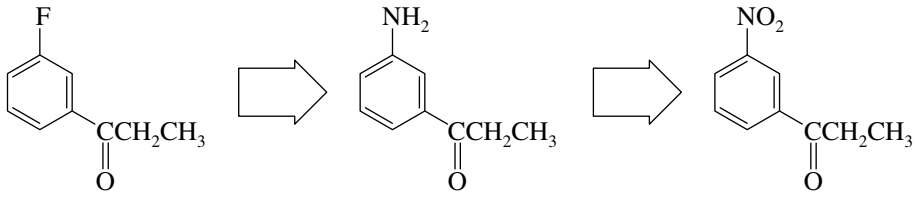
m-Bromoiodobenzene *m*-Bromoaniline

The preparation of *m*-bromoaniline from benzene has been described in Problem 22.17. All that remains is to write the equation for its conversion to *m*-bromoiodobenzene.



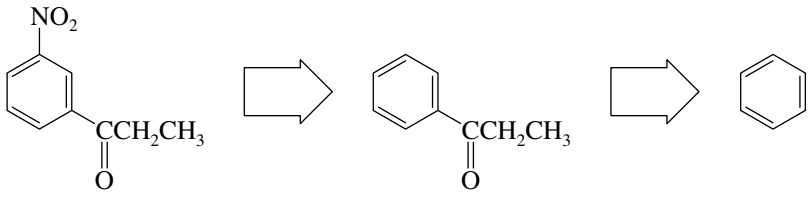
m-Bromoaniline *m*-Bromoiodobenzene

22.19 The final step in the preparation of ethyl *m*-fluorophenyl ketone is shown in the text example immediately preceding this problem, therefore all that is necessary is to describe the preparation of *m*-aminophenyl ethyl ketone.



Ethyl *m*-fluorophenyl ketone | *m*-Aminophenyl ethyl ketone | Ethyl *m*-nitrophenyl ketone

Recalling that arylamines are normally prepared by reduction of nitroarenes, we see that ethyl *m*-nitrophenyl ketone is a pivotal synthetic intermediate. It is prepared by nitration of ethyl phenyl ketone, which is analogous to nitration of acetophenone, shown in Section 12.16. The preparation of ethyl phenyl ketone by Friedel–Crafts acylation of benzene is shown in Section 12.7.

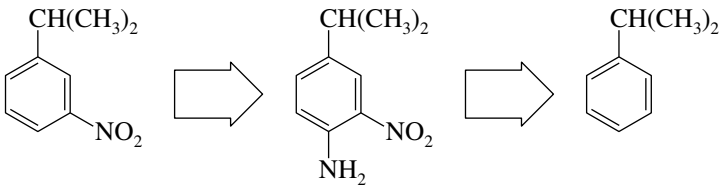


Ethyl *m*-nitrophenyl ketone | Ethyl phenyl ketone

Reversing the order of introduction of the nitro and acyl groups is incorrect. It is possible to nitrate ethyl phenyl ketone but not possible to carry out a Friedel–Crafts acylation on nitrobenzene, owing to the strong deactivating influence of the nitro group.

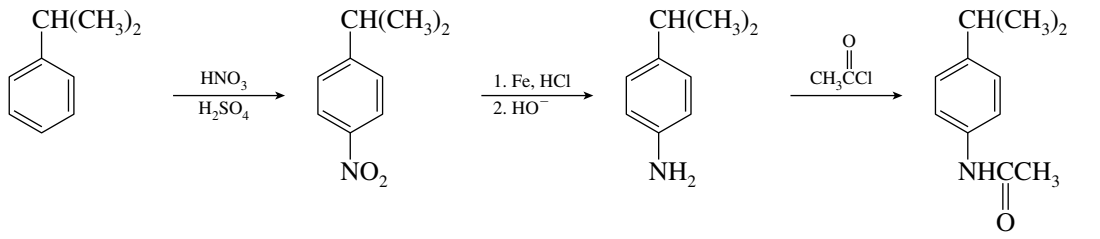
22.20 Direct nitration of the prescribed starting material cumene (isopropylbenzene) is not suitable, because isopropyl is an ortho, para-directing substituent and will give the target molecule

m-nitrocumene as only a minor component of the nitration product. However, the conversion of 4-isopropyl-2-nitroaniline to *m*-isopropylnitrobenzene, which was used to illustrate reductive deamination of arylamines in the text, establishes the last step in the synthesis.

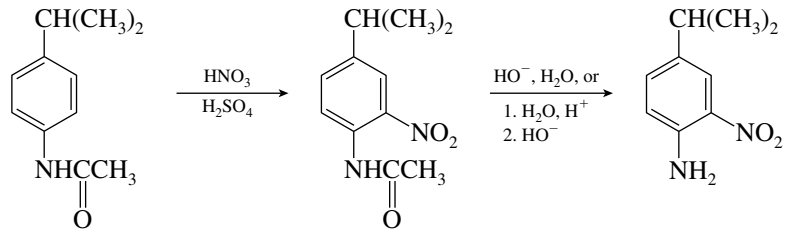


m-Nitrocumene | 4-Isopropyl-2-nitroaniline | Cumene

Our task simplifies itself to the preparation of 4-isopropyl-2-nitroaniline from cumene. The following procedure is a straightforward extension of the reactions and principles developed in this chapter.



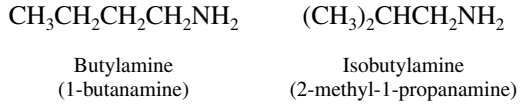
Cumene | *p*-Nitrocumene | *p*-Isopropylaniline | *p*-Isopropylacetanilide



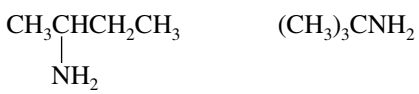
p-Isopropylacetanilide | 4-Isopropyl-2-nitroacetanilide | 4-Isopropyl-2-nitroaniline

Reductive deamination of 4-isopropyl-2-nitroaniline by diazotization in the presence of ethanol or hypophosphorous acid yields *m*-nitrocumene and completes the synthesis.

22.21 Amines may be primary, secondary, or tertiary. The $C_4H_{11}N$ primary amines, compounds of the type $C_4H_9NH_2$, and their systematic names are

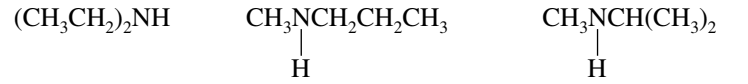


Butylamine (1-butanamine) | Isobutylamine (2-methyl-1-propanamine)



sec-Butylamine (2-butanamine) | *tert*-Butylamine (2-methyl-2-propanamine)

Secondary amines have the general formula R_2NH. Those of molecular formula $C_4H_{11}N$ are

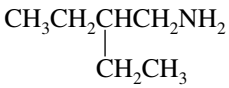


Diethylamine (*N*-ethylethanamine) | *N*-Methylpropylamine (*N*-methyl-1-propanamine) | *N*-Methylisopropylamine (*N*-methyl-2-propanamine)

There is only one tertiary amine (R_3N) of molecular formula $C_4H_{11}N$:

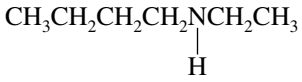
N,*N*-Dimethylethylamine (*N*,*N*-dimethylethanamine)

22.22 (*a*) The name 2-ethyl-1-butanamine designates a four-carbon chain terminating in an amino group and bearing an ethyl group at C-2.



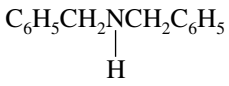
2-Ethyl-1-butanamine

(*b*) The prefix *N*- in *N*-ethyl-1-butanamine identifies the ethyl group as a substituent on nitrogen in a secondary amine.



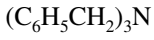
N-Ethyl-1-butanamine

(*c*) Dibenzylamine is a secondary amine. It bears two benzyl groups on nitrogen.



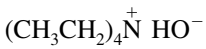
Dibenzylamine

(*d*) Tribenzylamine is a tertiary amine.



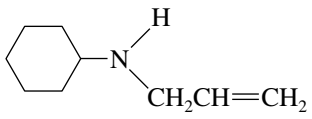
Tribenzylamine

(*e*) Tetraethylammonium hydroxide contains a quaternary ammonium ion.



Tetraethylammonium hydroxide

(*f*) This compound is a secondary amine; it bears an allyl substituent on the nitrogen of cyclohexylamine.

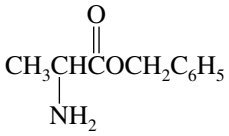


N-Allylcyclohexylamine

(*g*) Piperidine is a cyclic secondary amine that contains nitrogen in a six-membered ring. *N*-Allylpiperidine is a tertiary amine.

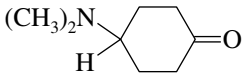
N-Allylpiperidine

(*h*) The compound is the benzyl ester of 2-aminopropanoic acid.



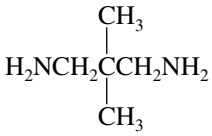
Benzyl 2-aminopropanoate

(*i*) The parent compound is cyclohexanone. The substituent $(CH_3)_2N$— group is attached to C-4.



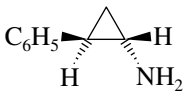
4-(*N*,*N*-Dimethylamino)-cyclohexanone

(*j*) The suffix *-diamine* reveals the presence of two amino groups, one at either end of a three-carbon chain that bears two methyl groups at C-2.



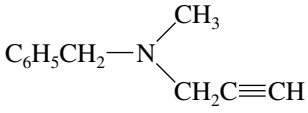
2,2-Dimethyl-1,3-propanediamine

22.23 (*a*) A phenyl group and an amino group are trans to each other on a three-membered ring in this compound.



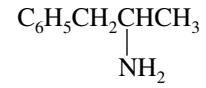
trans-2-Phenylcyclopropylamine (tranylcypromine)

(*b*) This compound is a tertiary amine. It bears a benzyl group, a methyl group, and a 2-propynyl group on nitrogen.



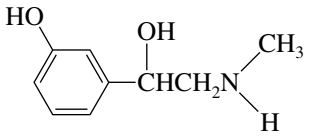
N-Benzyl-*N*-methyl-2-propynylamine (pargyline)

(*c*) The amino group is at C-2 of a three-carbon chain that bears a phenyl substituent at its terminus.



1-Phenyl-2-propanamine
(amphetamine)

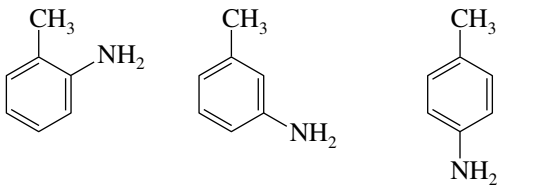
(*d*) Phenylephrine is named systematically as an ethanol derivative.



1-(*m*-Hydroxyphenyl)-
2-(methylamino)ethanol

22.24 (*a*) There are five isomers of C_7H_9N that contain a benzene ring.

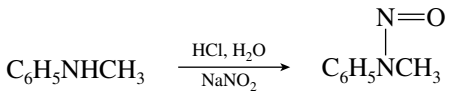
Benzylamine *N*-Methylaniline



o-Methylaniline *m*-Methylaniline *p*-Methylaniline

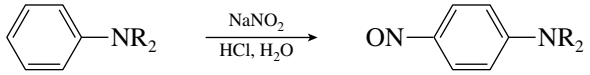
(*b*) Benzylamine is the strongest base because its amine group is bonded to an sp^3-hybridized carbon. Benzylamine is a typical alkylamine, with a K_b of 2×10^{-5}. All the other isomers are arylamines, with K_b values in the 10^{-10} range.

(*c*) The formation of *N*-nitrosoamines on reaction with sodium nitrite and hydrochloric acid is a characteristic reaction of secondary amines. The only C_7H_9N isomer in this problem that is a secondary amine is *N*-methylaniline.



N-Methylaniline *N*-Methyl-*N*-
nitrosoaniline

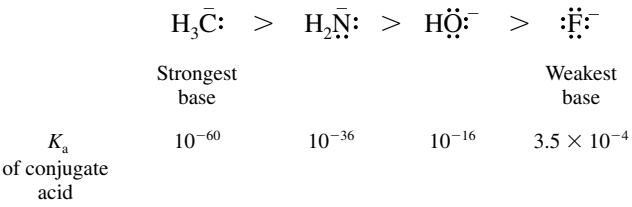
(*d*) Ring nitrosation is a characteristic reaction of tertiary arylamines.



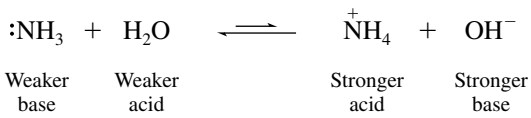
Tertiary arylamine *p*-Nitroso-*N*,*N*-dialkylaniline

None of the C_7H_9N isomers in this problem is a tertiary amine; hence none will undergo ring nitrosation.

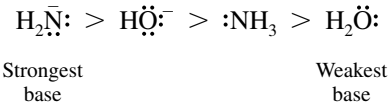
22.25 (*a*) Basicity decreases in proceeding across a row in the periodic table. The increased nuclear charge as one progresses from carbon to nitrogen to oxygen to fluorine causes the electrons to be bound more strongly to the atom and thus less readily shared.



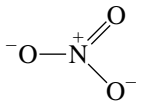
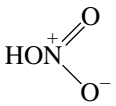
(*b*) The strongest base in this group is amide ion, H_2N^-, and the weakest base is water, H_2O. Ammonia is a weaker base than hydroxide ion; the equilibrium lies to the left.



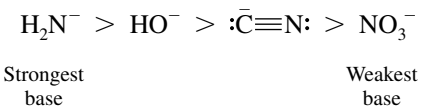
The correct order is



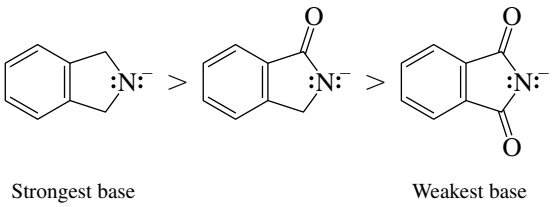
(*c*) These anions can be ranked according to their basicity by considering the respective acidities of their conjugate acids.

Base	Conjugate acid	K_a of conjugate acid
H_2N^-	H_3N	10^{-36}
HO^-	H_2O	10^{-16}
$^-:C{\equiv}N:$	$HC{\equiv}N:$	7.2×10^{-10}
		2.5×10^{1}

The order of basicities is the opposite of the order of acidities of their conjugate acids.



(*d*) A carbonyl group attached to nitrogen stabilizes its negative charge. The strongest base is the anion that has no carbonyl groups on nitrogen; the weakest base is phthalimide anion, which has two carbonyl groups.



22.26 (*a*) An alkyl substituent on nitrogen is electron-releasing and base-strengthening; thus methylamine is a stronger base than ammonia. An aryl substituent is electron-withdrawing and base-weakening, and so aniline is a weaker base than ammonia.

$$CH_3NH_2 \quad > \quad NH_3 \quad > \quad C_6H_5NH_2$$

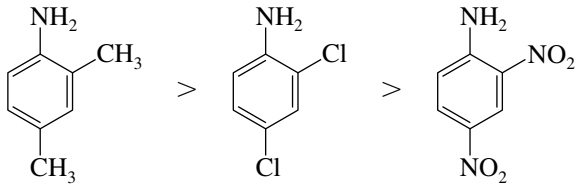
Methylamine, strongest base:	Ammonia:	Aniline, weakest base:
K_b 4.4×10^{-4}	K_b 1.8×10^{-5}	K_b 3.8×10^{-10}
pK_b 3.4	pK_b 4.7	pK_b 9.4

(*b*) An acetyl group is an electron-withdrawing and base-weakening substituent, especially when bonded directly to nitrogen. Amides are weaker bases than amines, and thus acetanilide is a weaker base than aniline. Alkyl groups are electron-releasing; *N*-methylaniline is a slightly stronger base than aniline.

$$C_6H_5NHCH_3 \quad > \quad C_6H_5NH_2 \quad > \quad C_6H_5NHC(=O)CH_3$$

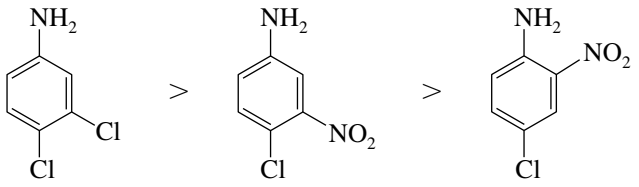
N-methylaniline, strongest base:	Aniline:	Acetanilide, weakest base:
K_b 8×10^{-10}	K_b 3.8×10^{-10}	K_b 1×10^{-15}
pK_b 9.1	pK_b 9.4	pK_b 15.0

(*c*) Chlorine substituents are slightly electron-withdrawing, and methyl groups are slightly electron-releasing. 2,4-Dimethylaniline is therefore a stronger base than 2,4-dichloroaniline. Nitro groups are strongly electron-withdrawing, their base-weakening effect being especially pronounced when a nitro group is ortho or para to an amino group because the two groups are then directly conjugated.



2,4-Dimethylaniline, strongest base:	2,4-Dichloroaniline:	2,4-Dinitroaniline, weakest base:
K_b 8×10^{-10}	K_b 1×10^{-12}	K_b 3×10^{-19}
pK_b 9.1	pK_b 12.0	pK_b 18.5

(*d*) Nitro groups are more electron-withdrawing than chlorine, and the base-weakening effect of a nitro substituent is greater when it is ortho or para to an amino group than when it is meta to it.



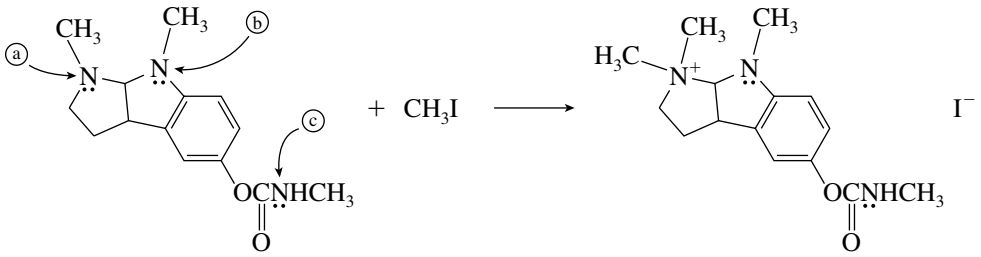
3,4-Dichloroaniline, strongest base:	4-Chloro-3-nitroaniline:	4-Chloro-2-nitroaniline, weakest base:
$K_b \approx 10^{-11}$	K_b 8×10^{-13}	K_b 1×10^{-15}
p$K_b \approx 11$	pK_b 12.1	pK_b 15.0

(*e*) According to the principle applied in part (*a*) (alkyl groups increase basicity, aryl groups decrease it), the order of decreasing basicity is as shown:

$$(CH_3)_2NH \;>\; C_6H_5NHCH_3 \;>\; (C_6H_5)_2NH$$

Dimethylamine, strongest base:	*N*-Methylaniline:	Diphenylamine, weakest base:
K_b 5.1×10^{-4}	K_b 8×10^{-10}	K_b 6×10^{-14}
pK_b 3.3	pK_b 9.1	pK_b 13.2

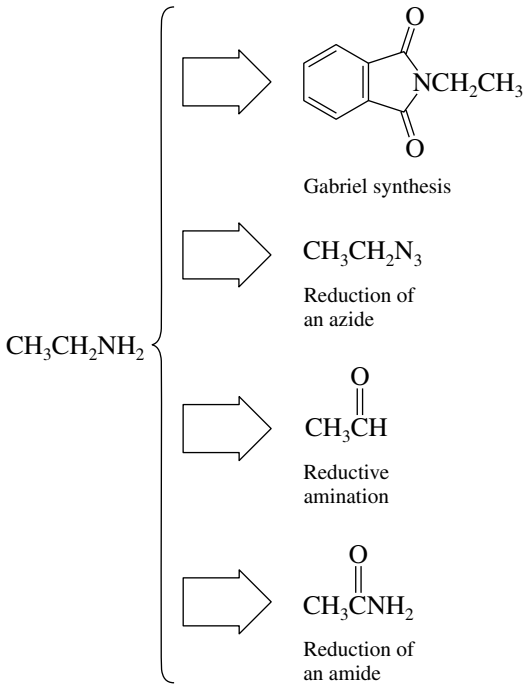
22.27 Nitrogen ⓐ is the most basic and the most nucleophilic of the three nitrogen atoms of physostigmine and is the one that reacts with methyl iodide.



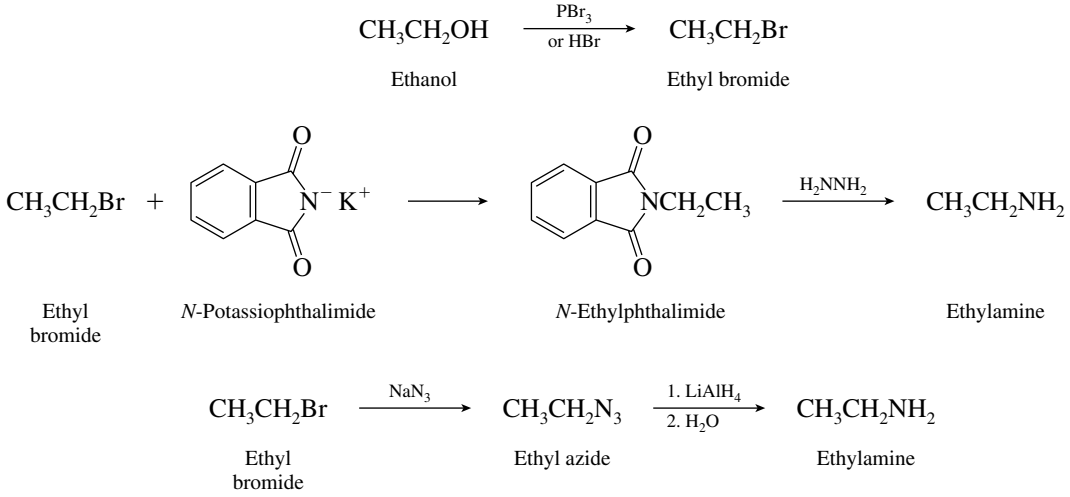
Physostigmine — Methyl iodide — "Physostigmine methiodide"

The nitrogen that reacts is the one that is a tertiary alkylamine. Of the other two nitrogens, ⓑ is attached to an aromatic ring and is much less basic and less nucleophilic. The third nitrogen, ⓒ, is an amide nitrogen; amides are less nucleophilic than amines.

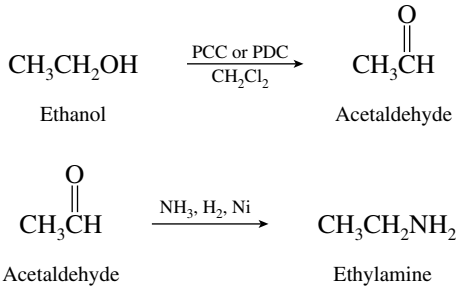
22.28 (*a*) Looking at the problem retrosynthetically, it can be seen that a variety of procedures are available for preparing ethylamine from ethanol. The methods by which a primary amine may be prepared include



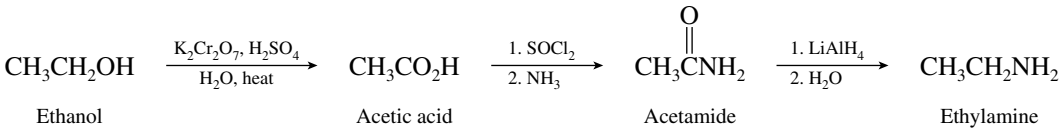
Two of these methods, the Gabriel synthesis and the preparation and reduction of the corresponding azide, begin with ethyl bromide.



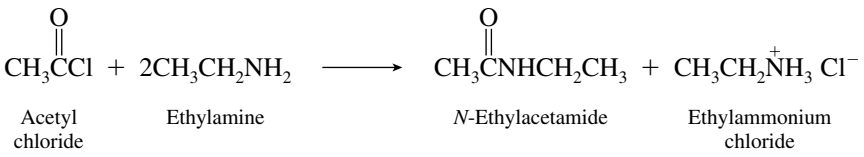
To use reductive amination, we must begin with oxidation of ethanol to acetaldehyde.



Another possibility is reduction of acetamide. This requires an initial oxidation of ethanol to acetic acid.

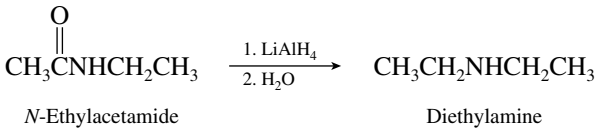


(*b*) Acylation of ethylamine with acetyl chloride, prepared in part (*a*), gives the desired amide.

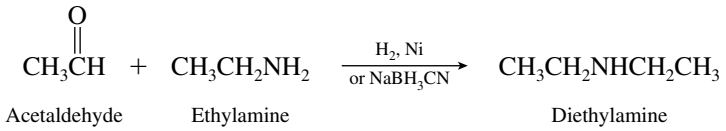


Excess ethylamine can be allowed to react with the hydrogen chloride formed in the acylation reaction. Alternatively, equimolar amounts of acyl chloride and amine can be used in the presence of aqueous hydroxide as the base.

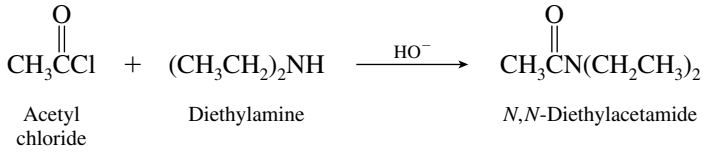
(*c*) Reduction of the *N*-ethylacetamide prepared in part (*b*) yields diethylamine.



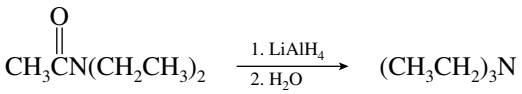
Diethylamine can also be prepared by reductive amination of acetaldehyde [from part (*a*)] with ethylamine.

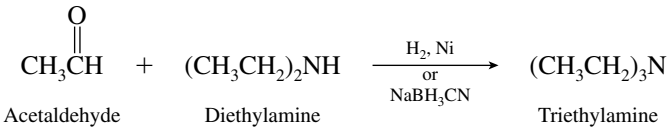


(*d*) The preparation of *N*,*N*-diethylacetamide is a standard acylation reaction. The reactants, acetyl chloride and diethylamine, have been prepared in previous parts of this problem.

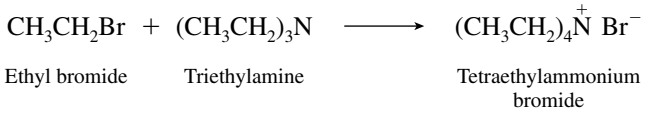


(*e*) Triethylamine arises by reduction of *N*,*N*-diethylacetamide or by reductive amination.

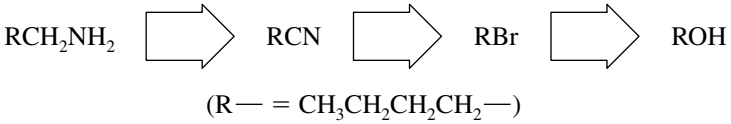




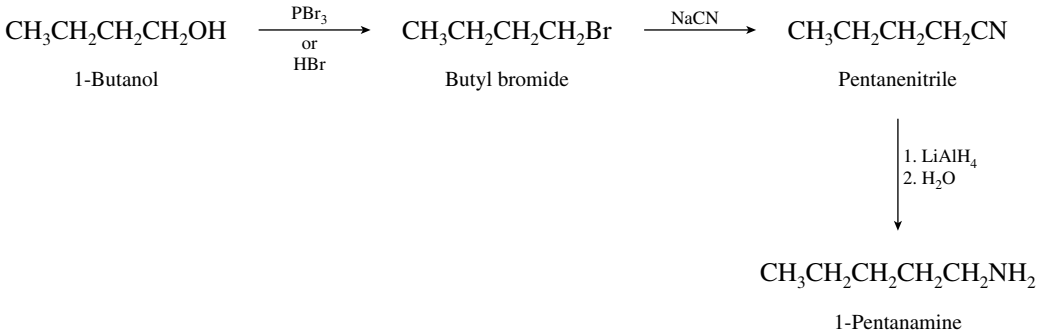
(*f*) Quaternary ammonium halides are formed by reaction of alkyl halides and tertiary amines.



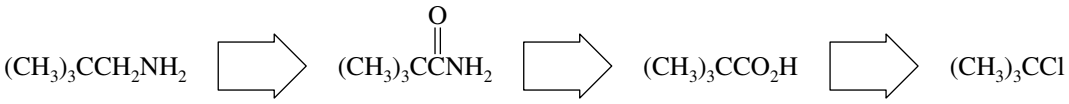
22.29 (*a*) In this problem a primary alkanamine must be prepared with a carbon chain extended by one carbon. This can be accomplished by way of a nitrile.



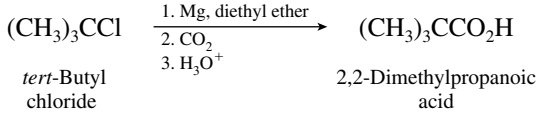
The desired reaction sequence is therefore



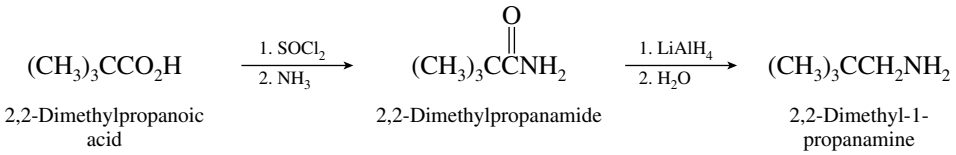
(*b*) The carbon chain of *tert*-butyl chloride cannot be extended by a nucleophilic substitution reaction; the S_N2 reaction that would be required on the tertiary halide would not work. The sequence employed in part (*a*) is therefore not effective in this case. The best route is carboxylation of the Grignard reagent and subsequent conversion of the corresponding amide to the desired primary amine product.



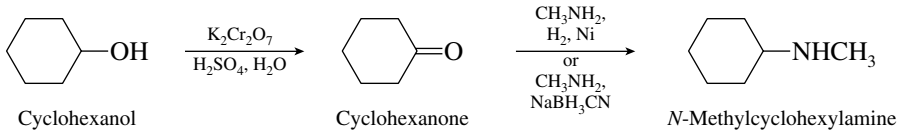
The reaction sequence to be used is



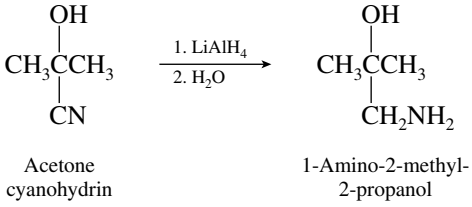
Once the carboxylic acid has been obtained, it is converted to the desired amine by reduction of the corresponding amide.



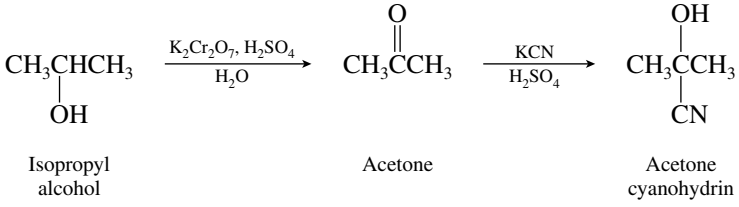
(*c*) Oxidation of cyclohexanol to cyclohexanone gives a compound suitable for reductive amination.



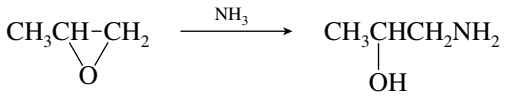
(*d*) The desired product is the reduction product of the cyanohydrin of acetone.



The cyanohydrin is made from acetone in the usual way. Acetone is available by oxidation of isopropyl alcohol.

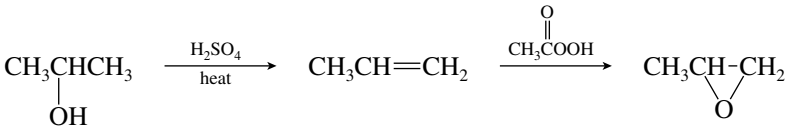


(*e*) The target amino alcohol is the product of nucleophilic ring opening of 1,2-epoxypropane by ammonia. Ammonia attacks the less hindered carbon of the epoxide function.



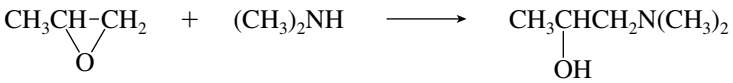
1,2-Epoxypropane — 1-Amino-2-propanol

The necessary epoxide is formed by epoxidation of propene.



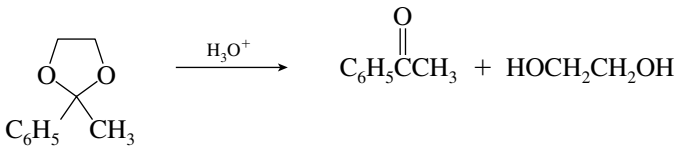
Isopropyl alcohol — Propene — 1,2-Epoxypropane

(*f*) The reaction sequence is the same as in part (*e*) except that dimethylamine is used as the nucleophile instead of ammonia.



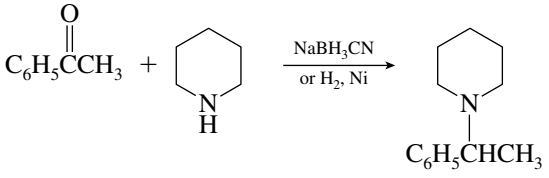
1,2-Epoxypropane [prepared as in part (*e*)] — Dimethylamine — 1-(*N*,*N*-Dimethylamino)-2-propanol

(*g*) The key to performing this synthesis is recognition of the starting material as an acetal of acetophenone. Acetals may be hydrolyzed to carbonyl compounds.



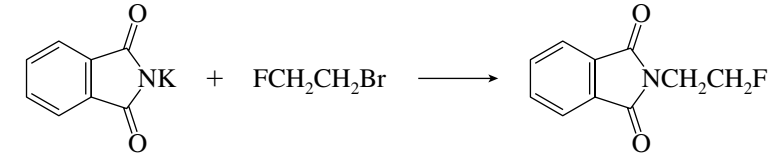
2-Methyl-2-phenyl-1,3-dioxolane — Acetophenone — 1,2-Ethanediol

Once acetophenone has been obtained, it may be converted to the required product by reductive amination.



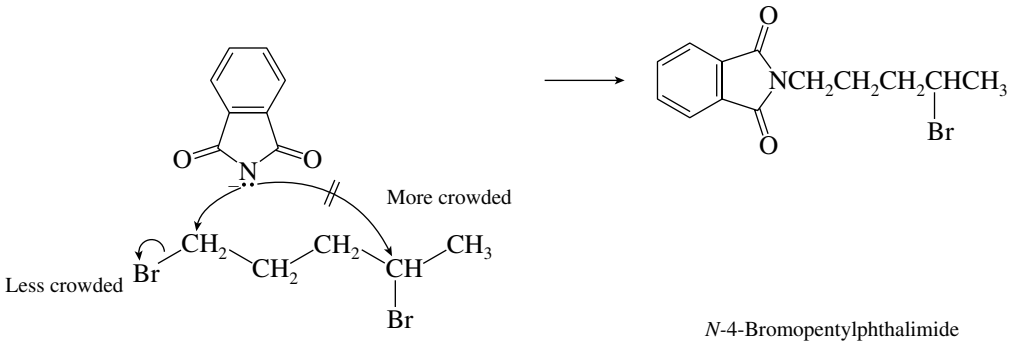
Acetophenone — Piperidine — *N*-(1-Phenylethyl)-piperidine

22.30 (*a*) The reaction of alkyl halides with *N*-potassiophthalimide (the first step in the Gabriel synthesis of amines) is a nucleophilic substitution reaction. Alkyl bromides are more reactive than alkyl fluorides; that is, bromide is a better leaving group than fluoride.



N-Potassiophthalimide — 1-Bromo-2-fluoroethane — 2-Phthalimidoethyl fluoride

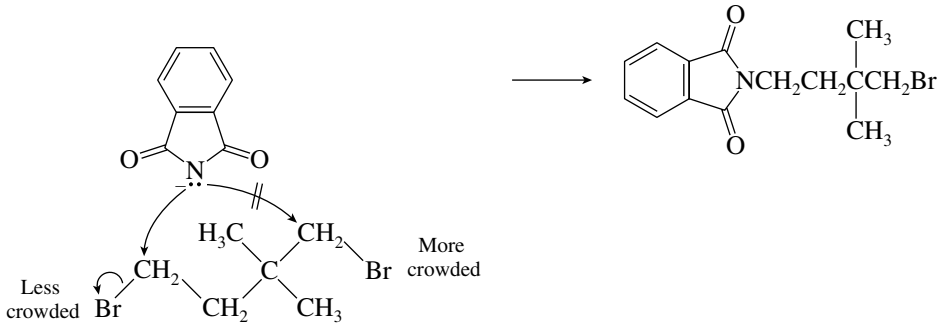
(*b*) In this example one bromine is attached to a primary and the other to a secondary carbon. Phthalimide anion is a good nucleophile and reacts with alkyl halides by the S_N2 mechanism. It attacks the less hindered primary carbon.



1,4-Dibromopentane

N-4-Bromopentylphthalimide
(only product, 67% yield)

(*c*) Both bromines are bonded to primary carbons, but branching at the adjacent carbon hinders nucleophilic attack at one of them.



1,4-Dibromo-2,2-dimethylbutane

N-4-Bromo-3,3-dimethylphthalimide
(only product, 53% yield)

22.31 (*a*) Amines are basic and are protonated by hydrogen halides.

$$C_6H_5CH_2NH_2 + HBr \longrightarrow C_6H_5CH_2\overset{+}{N}H_3\ Br^-$$

Benzylamine — Benzylammonium bromide

(*b*) Equimolar amounts of benzylamine and sulfuric acid yield benzylammonium hydrogen sulfate as the product.

$$C_6H_5CH_2NH_2 + HOSO_2OH \longrightarrow C_6H_5CH_2\overset{+}{N}H_3\ {}^-OSO_2OH$$

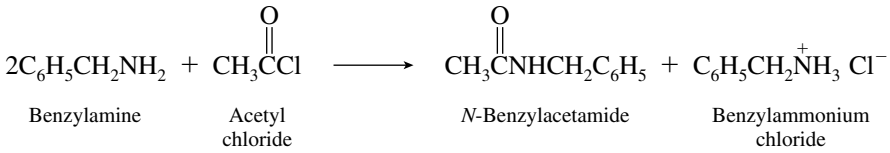
Benzylamine — Sulfuric acid — Benzylammonium hydrogen sulfate

(*c*) Acetic acid transfers a proton to benzylamine.

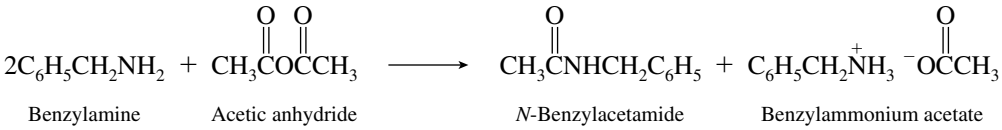
$$C_6H_5CH_2NH_2 + CH_3\overset{O}{\overset{\|}{C}}OH \longrightarrow C_6H_5CH_2\overset{+}{N}H_3\ {}^-O\overset{O}{\overset{\|}{C}}CH_3$$

Benzylamine — Acetic acid — Benzylammonium acetate

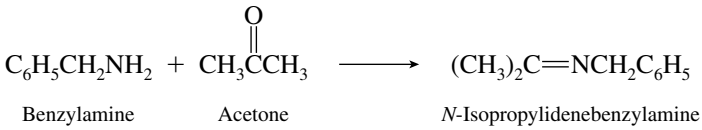
(*d*) Acetyl chloride reacts with benzylamine to form an amide.



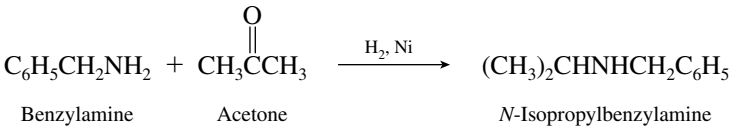
(*e*) Acetic anhydride also gives an amide with benzylamine.



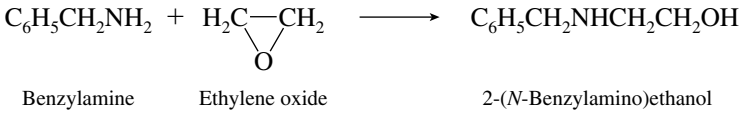
(*f*) Primary amines react with ketones to give imines.



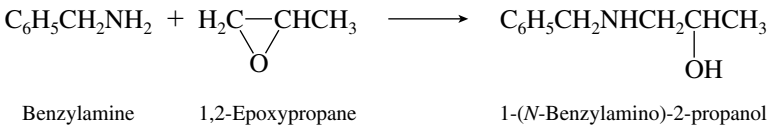
(*g*) These reaction conditions lead to reduction of the imine formed in part (*f*). The overall reaction is reductive amination.



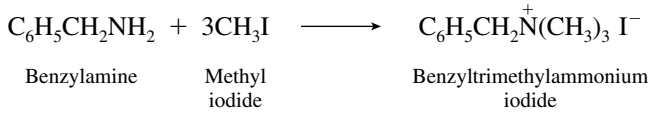
(*h*) Amines are nucleophilic and bring about the opening of epoxide rings.



(*i*) In these nucleophilic ring-opening reactions the amine attacks the less sterically hindered carbon of the ring.



(*j*) With excess methyl iodide, amines are converted to quaternary ammonium iodides.



(*k*) Nitrous acid forms from sodium nitrite in dilute hydrochloric acid. Nitrosation of benzylamine in water gives benzyl alcohol via a diazonium ion intermediate.

$$\underset{\text{Benzylamine}}{C_6H_5CH_2NH_2} \xrightarrow[H_2O]{NaNO_2,\ HCl} \underset{\text{Benzyldiazonium ion}}{C_6H_5CH_2\overset{+}{N}\equiv N} \xrightarrow[H_2O]{-N_2} \underset{\text{Benzyl alcohol}}{C_6H_5CH_2OH}$$

Benzyl chloride will also be formed by attack of chloride on the diazonium ion.

22.32 (*a*) Aniline is a weak base and yields a salt on reaction with hydrogen bromide.

$$\underset{\text{Aniline}}{C_6H_5NH_2} + \underset{\text{Hydrogen bromide}}{HBr} \longrightarrow \underset{\text{Anilinium bromide}}{C_6H_5\overset{+}{N}H_3\ Br^-}$$

(*b*) Aniline acts as a nucleophile toward methyl iodide. With excess methyl iodide, a quaternary ammonium salt is formed.

$$\underset{\text{Aniline}}{C_6H_5NH_2} + \underset{\text{Methyl iodide}}{3CH_3I} \longrightarrow \underset{\text{\textit{N},\textit{N},\textit{N}-Trimethylanilinium iodide}}{C_6H_5\overset{+}{N}(CH_3)_3\ I^-}$$

(*c*) Aniline is a primary amine and undergoes nucleophilic addition to aldehydes and ketones to form imines.

$$\underset{\text{Aniline}}{C_6H_5NH_2} + \underset{\text{Acetaldehyde}}{CH_3\overset{O}{\overset{\|}{C}}H} \longrightarrow \underset{\textit{N}\text{-Phenylacetaldimine}}{C_6H_5N{=}CHCH_3} + \underset{\text{Water}}{H_2O}$$

(*d*) When an imine is formed in the presence of hydrogen and a suitable catalyst, reductive amination occurs to give an amine.

$$\underset{\text{Aniline}}{C_6H_5NH_2} + \underset{\text{Acetaldehyde}}{CH_3\overset{O}{\overset{\|}{C}}H} \xrightarrow{H_2,\ Ni} \underset{\textit{N}\text{-Ethylaniline}}{C_6H_5NHCH_2CH_3}$$

(*e*) Aniline undergoes *N*-acylation on treatment with carboxylic acid anhydrides.

$$\underset{\text{Aniline}}{2C_6H_5NH_2} + \underset{\text{Acetic anhydride}}{CH_3\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}CH_3} \longrightarrow \underset{\text{Acetanilide}}{C_6H_5NH\overset{O}{\overset{\|}{C}}CH_3} + \underset{\text{Anilinium acetate}}{C_6H_5\overset{+}{N}H_3\ {}^-O\overset{O}{\overset{\|}{C}}CH_3}$$

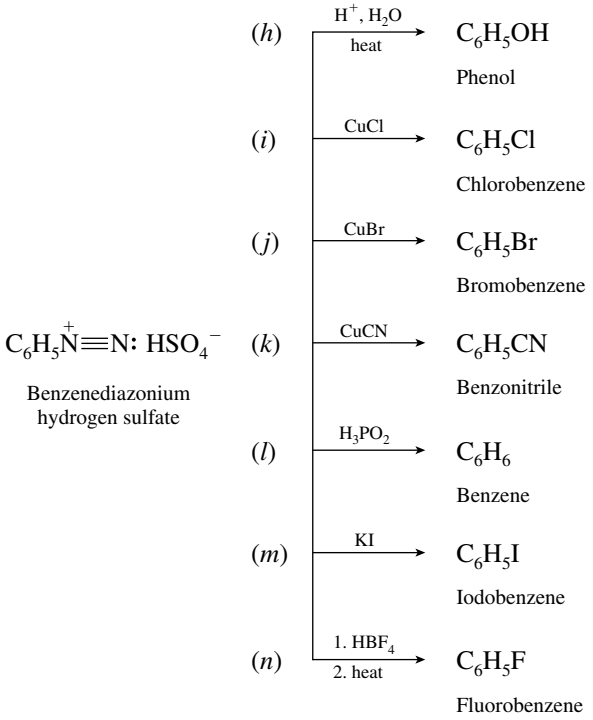
(*f*) Acyl chlorides bring about *N*-acylation of arylamines.

$$\underset{\text{Aniline}}{2C_6H_5NH_2} + \underset{\text{Benzoyl chloride}}{C_6H_5\overset{O}{\overset{\|}{C}}Cl} \longrightarrow \underset{\text{Benzanilide}}{C_6H_5NH\overset{O}{\overset{\|}{C}}C_6H_5} + \underset{\text{Anilinium chloride}}{C_6H_5\overset{+}{N}H_3\ Cl^-}$$

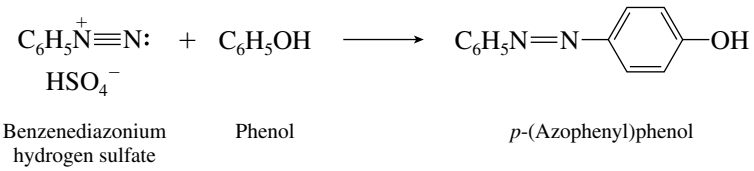
(*g*) Nitrosation of primary arylamines yields aryl diazonium salts.

$$\underset{\text{Aniline}}{C_6H_5NH_2} \xrightarrow[H_2O,\ 0\text{–}5^\circ C]{NaNO_2,\ H_2SO_4} \underset{\text{Benzenediazonium hydrogen sulfate}}{C_6H_5\overset{+}{N}{\equiv}N{:}\ HSO_4^-}$$

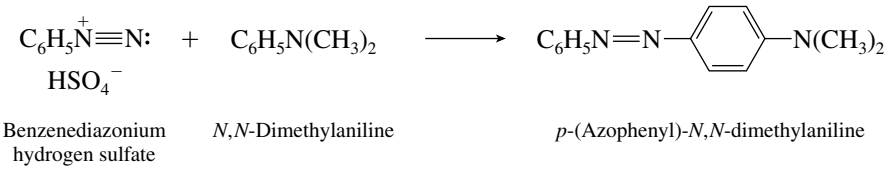
The replacement reactions that can be achieved by using diazonium salts are illustrated in parts (*h*) through (*n*). In all cases molecular nitrogen is lost from the ring carbon to which it was attached and is replaced by another substituent.



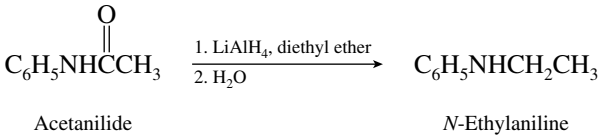
(*o*) The nitrogens of an aryl diazonium salt are retained on reaction with the electron-rich ring of a phenol. Azo coupling occurs.



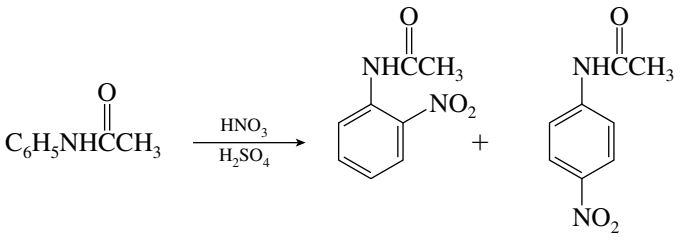
(*p*) Azo coupling occurs when aryl diazonium salts react with *N*,*N*-dialkylarylamines.



22.33 (*a*) Amides are reduced to amines by lithium aluminum hydride.

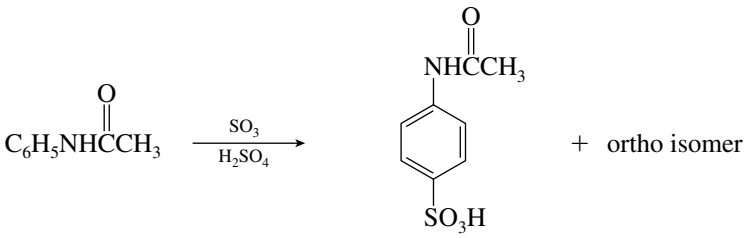


(*b*) Acetanilide is a reactive substrate toward electrophilic aromatic substitution. An acetamido group is ortho, para-directing.



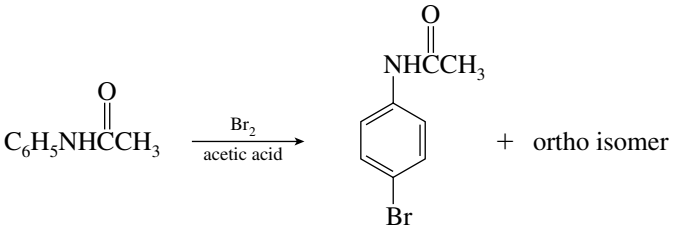
Acetanilide *o*-Nitroacetanilide *p*-Nitroacetanilide

(*c*) Sulfonation of the ring occurs.



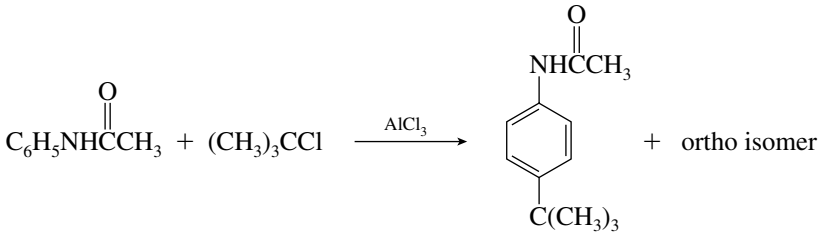
Acetanilide *p*-Acetamidobenzenesulfonic acid

(*d*) Bromination of the ring takes place.



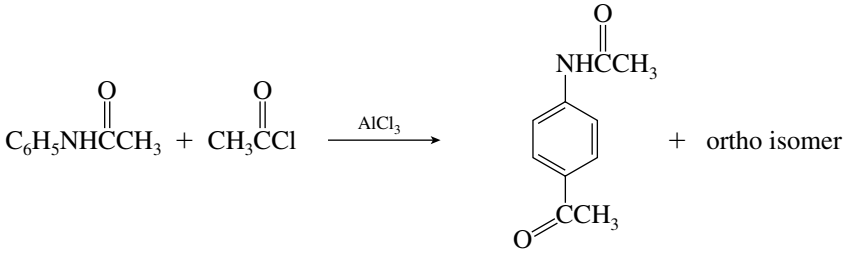
Acetanilide *p*-Bromoacetanilide

(*e*) Acetanilide undergoes Friedel–Crafts alkylation readily.



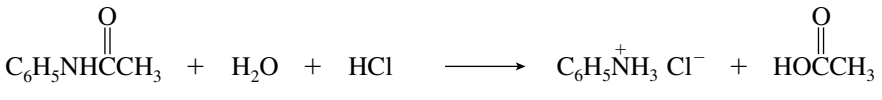
Acetanilide *tert*-Butyl chloride *p-tert*-Butylacetanilide

(*f*) Friedel–Crafts acylation also is easily carried out.

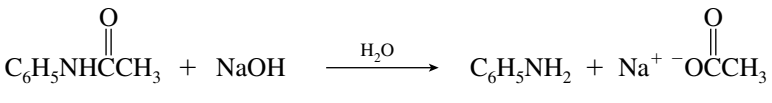


Acetanilide Acetyl chloride *p*-Acetamidoacetophenone

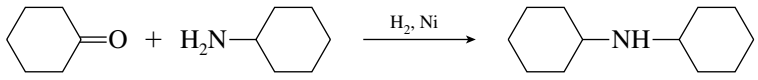
(*g*) Acetanilide is an amide and can be hydrolyzed when heated with aqueous acid. Under acidic conditions the aniline that is formed exists in its protonated form as the anilinium cation.



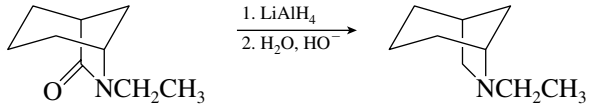
(*h*) Amides are hydrolyzed in base.



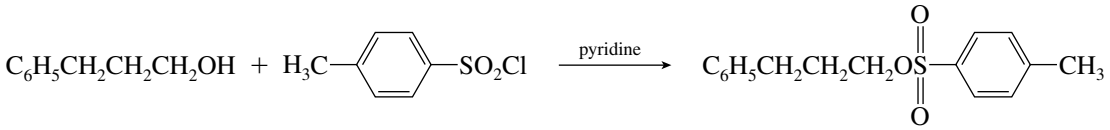
22.34 (*a*) The reaction illustrates the preparation of a secondary amine by reductive amination.



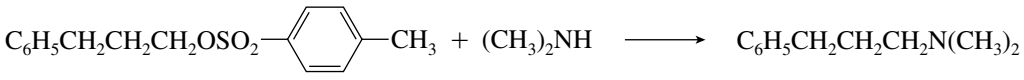
(*b*) Amides are reduced to amines by lithium aluminum hydride.



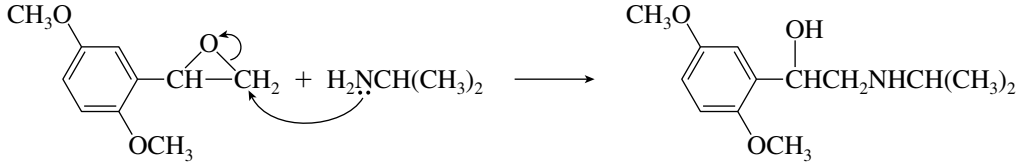
(*c*) Treatment of alcohols with *p*-toluenesulfonyl chloride converts them to *p*-toluenesulfonate esters.



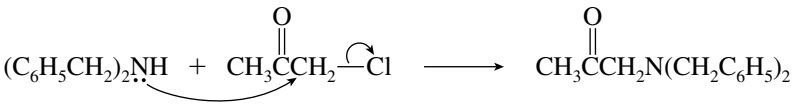
p-Toluenesulfonate is an excellent leaving group in nucleophilic substitution reactions. Dimethylamine is the nucleophile.



(*d*) Amines are sufficiently nucleophilic to react with epoxides. Attack occurs at the less substituted carbon of the epoxide.



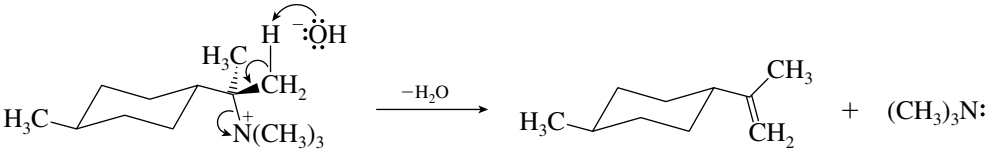
(*e*) α-Halo ketones are reactive substrates in nucleophilic substitution reactions. Dibenzylamine is the nucleophile.



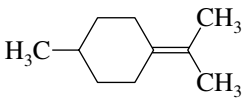
Dibenzylamine — 1-Chloro-2-propanone — 1-(Dibenzylamino)-2-propanone (87%)

Because the reaction liberates hydrogen chloride, it is carried out in the presence of added base—in this case triethylamine—so as to avoid converting the dibenzylamine to its hydrochloride salt.

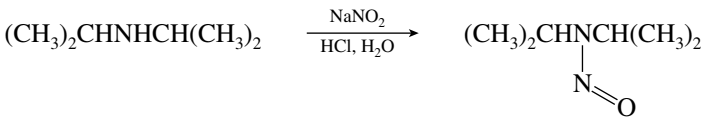
(*f*) Quaternary ammonium hydroxides undergo Hofmann elimination when they are heated. A point to be considered here concerns the regioselectivity of Hofmann eliminations: it is the less hindered β proton that is removed by the base giving the less substituted alkene.



trans-1-Isopropenyl-4-methylcyclohexane (98%) — Trimethylamine

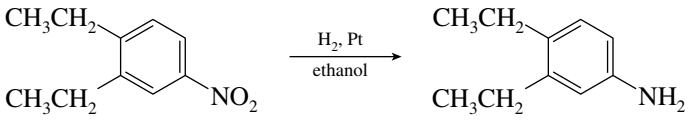
Elimination to give  does not occur.

(*g*) The combination of sodium nitrite and aqueous acid is a nitrosating agent. Secondary alkylamines react with nitrosating agents to give *N*-nitroso amines as the isolated products.



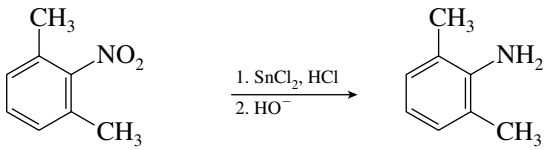
Diisopropylamine — *N*-Nitrosodiisopropylamine (91%)

22.35 (*a*) Catalytic hydrogenation reduces nitro groups to amino groups.



1,2-Diethyl-4-nitrobenzene — 3,4-Diethylaniline (93–99%)

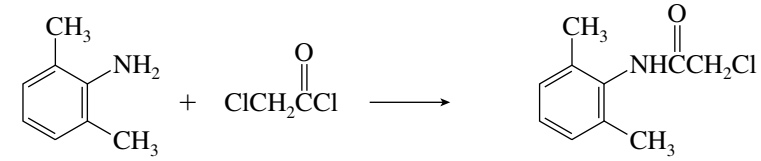
(*b*) Nitro groups are readily reduced by tin(II) chloride.



1,3-Dimethyl-2-nitrobenzene — 2,6-Dimethylaniline

This reaction is the first step in a synthesis of the drug **lidocaine.**

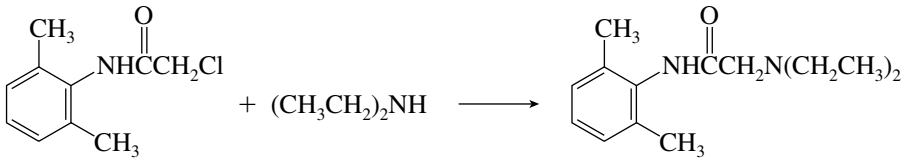
(*c*) The amino group of arylamines is nucleophilic and undergoes acylation on reaction with chloroacetyl chloride.



2,6-Dimethylaniline — Chloroacetyl chloride — *N*-(Chloroacetyl)-2,6-dimethylaniline

Chloroacetyl chloride is a difunctional compound—it is both an acyl chloride and an alkyl chloride. Acyl chlorides react with nucleophiles faster than do alkyl chlorides, so that acylation of the amine nitrogen occurs rather than alkylation.

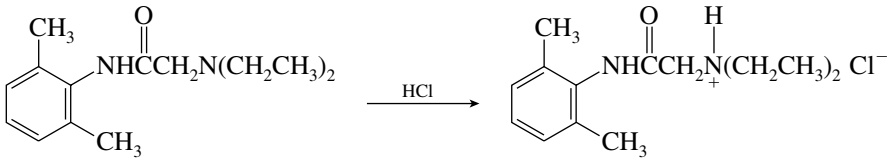
(*d*) The final step in the synthesis of lidocaine is displacement of the chloride by diethylamine from the α-halo amide formed in part (*c*) in a nucleophilic substitution reaction.



N-(Chloroacetyl)-2,6-dimethylaniline — Diethylamine — Lidocaine

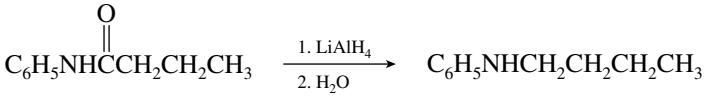
The reaction is carried out with excess diethylamine, which acts as a base to neutralize the hydrogen chloride formed.

(*e*) For use as an anesthetic, lidocaine is made available as its hydrochloride salt. Of the two nitrogens in lidocaine, the amine nitrogen is more basic than the amide.



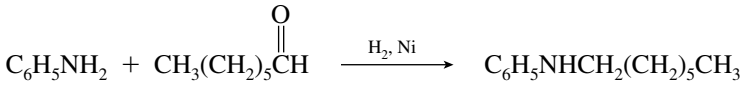
Lidocaine — Lidocaine hydrochloride

(*f*) Lithium aluminum hydride reduction of amides is one of the best methods for the preparation of amines, including arylamines.



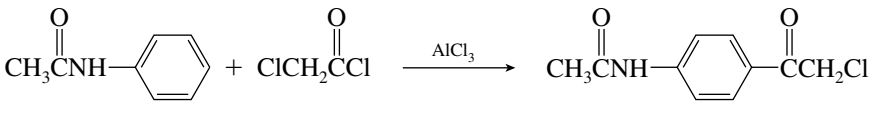
N-Phenylbutanamide — *N*-Butylaniline (92%)

(*g*) Arylamines react with aldehydes and ketones in the presence of hydrogen and nickel to give the product of reductive amination.



Aniline — Heptanal — *N*-Heptylaniline (65%)

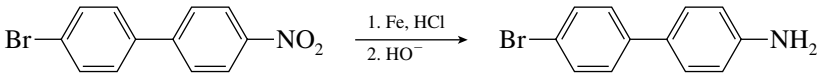
(*h*) Acetanilide is a reactive substrate toward electrophilic aromatic substitution. On reaction with chloroacetyl chloride, it undergoes Friedel–Crafts acylation, primarily at its para position.



Acetanilide — Chloroacetyl chloride — *p*-Acetamidophenacyl chloride (79–83%)

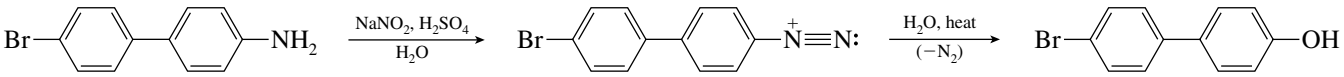
Acylation, rather than alkylation, occurs. Acyl chlorides are more reactive than alkyl chlorides toward electrophilic aromatic substitution reactions as a result of the more stable intermediate (acylium ion) formed.

(*i*) Reduction with iron in hydrochloric acid is one of the most common methods for converting nitroarenes to arylamines.



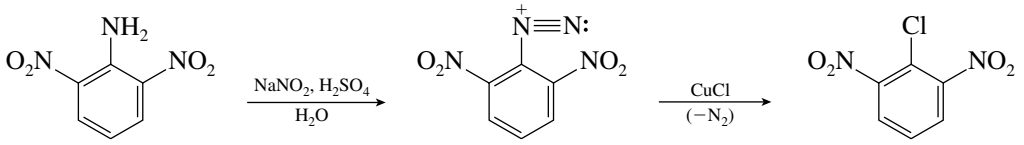
4-Bromo-4′-nitrobiphenyl — 4-Amino-4′-bromobiphenyl (94%)

(*j*) Primary arylamines are converted to aryl diazonium salts on treatment with sodium nitrite in aqueous acid. When the aqueous acidic solution containing the diazonium salt is heated, a phenol is formed.



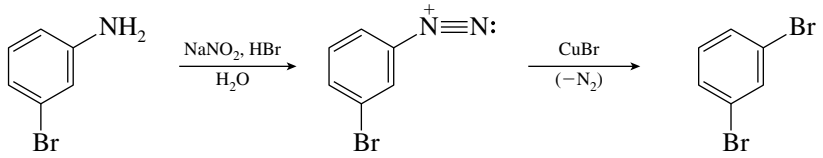
4-Amino-4′-bromobiphenyl — 4-Bromo-4′-hydroxybiphenyl (85%)

(*k*) This problem illustrates the conversion of an arylamine to an aryl chloride by the Sandmeyer reaction.



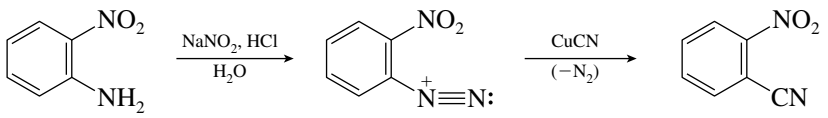
2,6-Dinitroaniline — 2-Chloro-1,3-dinitrobenzene (71–74%)

(*l*) Diazotization of primary arylamines followed by treatment with copper(I) bromide converts them to aryl bromides.



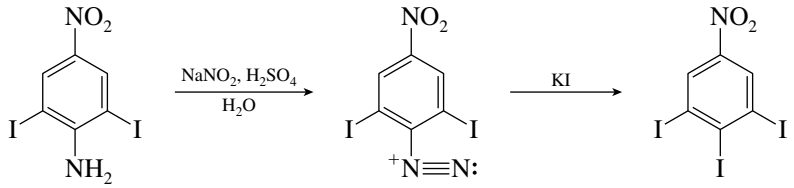
m-Bromoaniline — *m*-Dibromobenzene (80–87%)

(*m*) Nitriles are formed when aryl diazonium salts react with copper(I) cyanide.



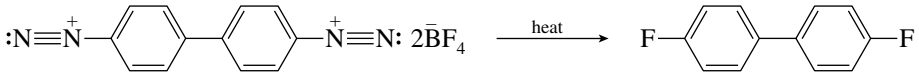
o-Nitroaniline — *o*-Nitrobenzonitrile (87%)

(*n*) An aryl diazonium salt is converted to an aryl iodide on reaction with potassium iodide.



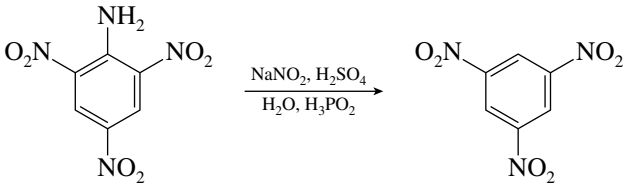
2,6-Diiodo-4-nitroaniline — 1,2,3-Triiodo-5-nitrobenzene (94–95%)

(*o*) Aryl diazonium fluoroborates are converted to aryl fluorides when heated. Both diazonium salt functions in the starting material undergo this reaction.



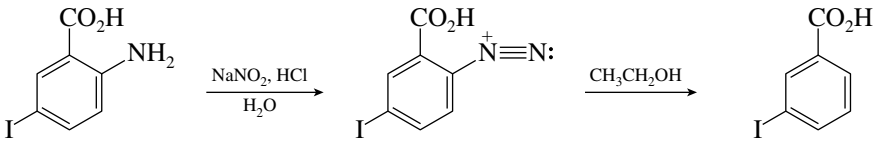
4,4′-Bis(diazonio)biphenyl fluoroborate — 4,4′-Difluorobiphenyl (82%)

(*p*) Hypophosphorous acid (H_3PO_2) reduces aryl diazonium salts to arenes.



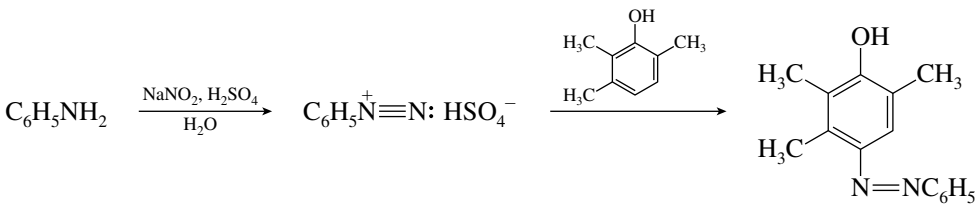
2,4,6-Trinitroaniline — 1,3,5-Trinitrobenzene (60–65%)

(*q*) Ethanol, like hypophosphorous acid, is an effective reagent for the reduction of aryl diazonium salts.



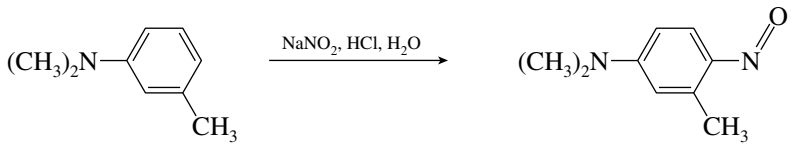
2-Amino-5-iodobenzoic acid — *m*-Iodobenzoic acid (86–93%)

(*r*) Diazotization of aniline followed by addition of a phenol yields a bright-red diazo-substituted phenol. The diazonium ion acts as an electrophile toward the activated aromatic ring of the phenol.



Aniline — Benzenediazonium hydrogen sulfate — 2,3,6-Trimethyl-4-(phenylazo)phenol (98%)

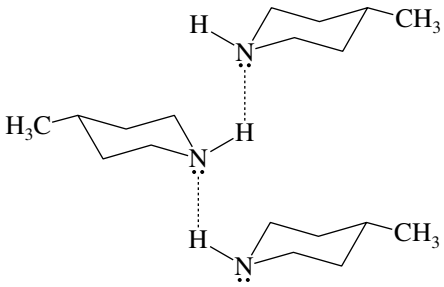
(*s*) Nitrosation of *N*,*N*-dialkylarylamines takes place on the ring at the position para to the dialkylamino group.



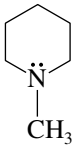
N,*N*-Dimethyl-*m*-toluidine

3-Methyl-4-nitroso-*N*,*N*-dimethylaniline (83%)

22.36 (*a*) 4-Methylpiperidine can participate in intermolecular hydrogen bonding in the liquid phase.

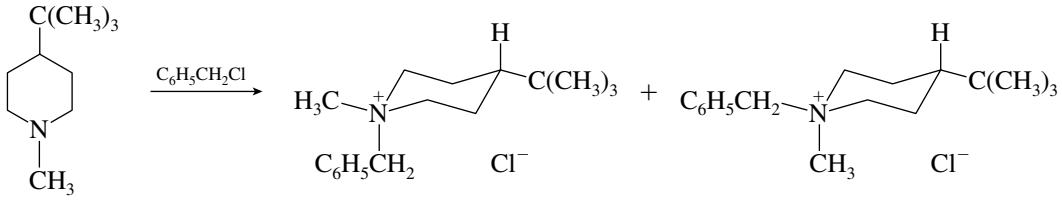


These hydrogen bonds must be broken in order for individual 4-methylpiperidine molecules to escape into the gas phase. *N*-Methylpiperidine lacks a proton bonded to nitrogen and so cannot engage in intermolecular hydrogen bonding. Less energy is required to transfer a molecule of *N*-methylpiperidine to the gaseous state, and therefore it has a lower boiling point than 4-methylpiperidine.



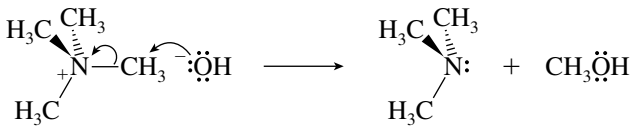
N-Methylpiperidine;
no hydrogen bonding possible
to other *N*-methylpiperidine molecules

(*b*) The two products are diastereomeric quaternary ammonium chlorides that differ in the configuration at the nitrogen atom.



4-*tert*-Butyl-*N*-methylpiperidine

(*c*) Tetramethylammonium hydroxide cannot undergo Hofmann elimination. The only reaction that can take place is nucleophilic substitution.

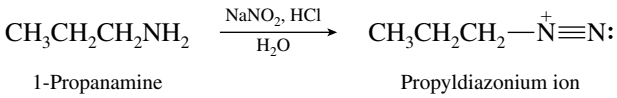


Tetramethylammonium hydroxide

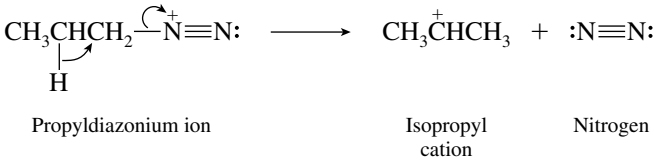
Trimethylamine

Methanol

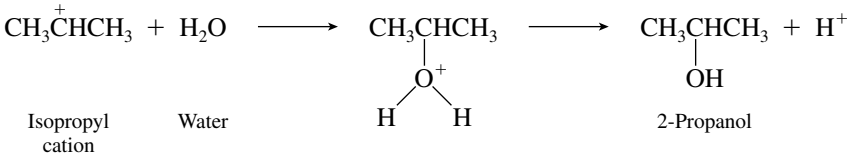
(*d*) The key intermediate in the reaction of an amine with nitrous acid is the corresponding diazonium ion.



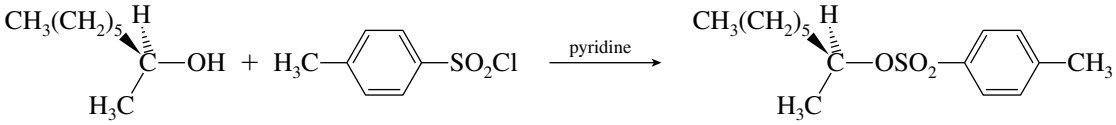
Loss of nitrogen from this diazonium ion is accompanied by a hydride shift to form a secondary carbocation.



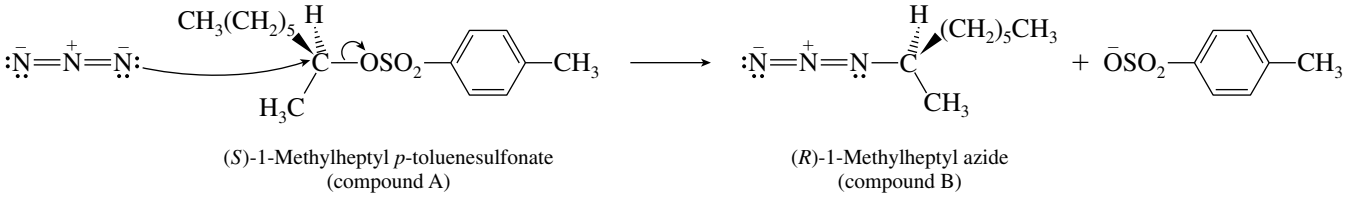
Capture of isopropyl cation by water yields the major product of the reaction, 2-propanol.



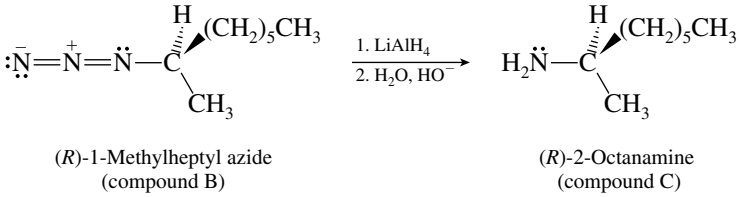
22.37 Alcohols are converted to *p*-toluenesulfonate esters by reaction with *p*-toluenesulfonyl chloride. None of the bonds to the stereogenic center is affected in this reaction.



Displacement of the *p*-toluenesulfonate leaving group by sodium azide in an S_N2 process and proceeds with inversion of configuration.

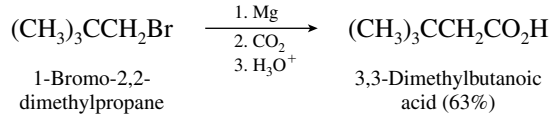


Reduction of the azide yields a primary amine. A nitrogen–nitrogen bond is cleaved; all the bonds to the stereogenic center remain intact.

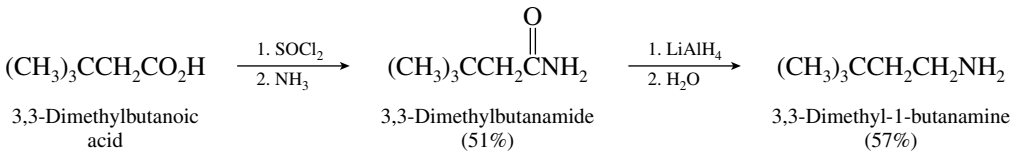


22.38 (*a*) The overall transformation can be expressed as RBr → RCH_2NH_2. In many cases this can be carried out via a nitrile, as RBr → RCN → RCH_2NH_2. In this case, however, the substrate is 1-bromo-2,2-dimethylpropane, an alkyl halide that reacts very slowly in nucleophilic substi-

tution processes. Carbon–carbon bond formation with 1-bromo-2,2-dimethylpropane can be achieved more effectively by carboxylation of the corresponding Grignard reagent.

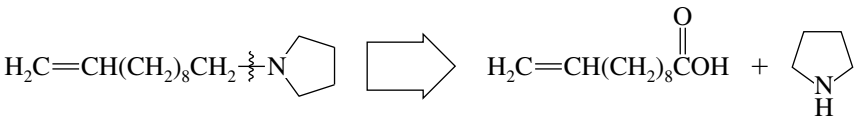


The carboxylic acid can then be converted to the desired amine by reduction of the derived amide.

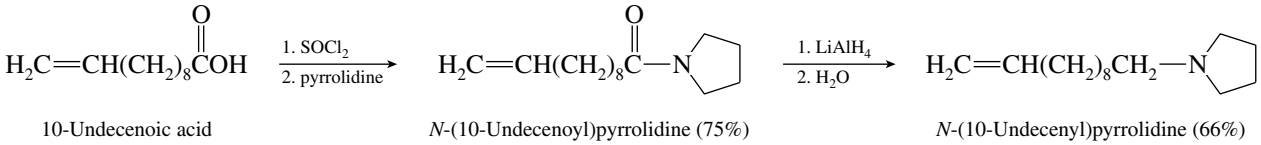


The yields listed in parentheses are those reported in the chemical literature for this synthesis.

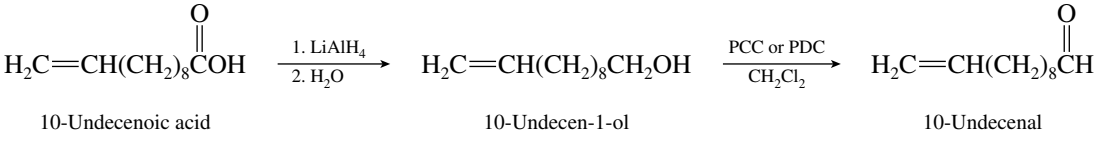
(*b*) Consider the starting materials in relation to the desired product.



The synthetic tasks are to form the necessary carbon–nitrogen bond and to reduce the carbonyl group to a methylene group. This has been accomplished by way of the amide as a key intermediate.



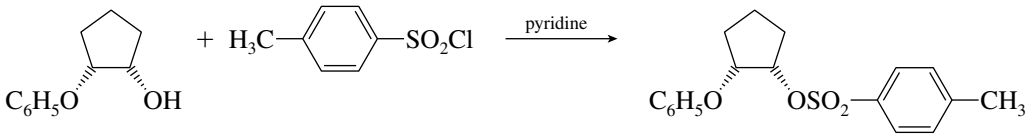
A second approach utilizes reductive amination following conversion of the starting carboxylic acid to an aldehyde.



The reducing agent in the reductive amination process cannot be hydrogen, because that would result in hydrogenation of the double bond. Sodium cyanoborohydride is required.

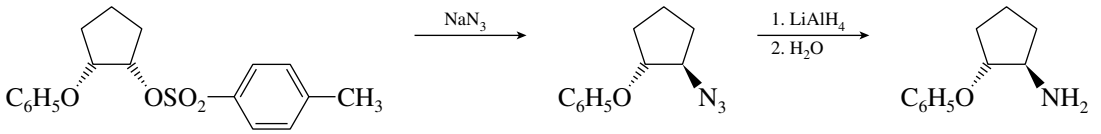
(*c*) It is stereochemistry that determines the choice of which synthetic method to employ in introducing the amine group. The carbon–nitrogen bond must be formed with inversion of

configuration at the alcohol carbon. Conversion of the alcohol to its *p*-toluenesulfonate ester ensures that the leaving group is introduced with exactly the same stereochemistry as the alcohol.



cis-2-Phenoxycyclopentanol — *p*-Toluenesulfonyl chloride — *cis*-2-Phenoxycyclopentyl *p*-toluenesulfonate

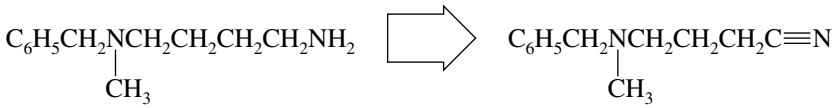
Once the leaving group has been introduced with the proper stereochemistry, it can be displaced by a nitrogen nucleophile suitable for subsequent conversion to an amine.



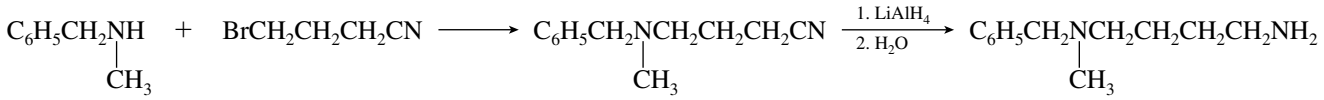
cis-2-Phenoxycyclopentyl *p*-toluenesulfonate — *trans*-2-Phenoxycyclopentyl azide (90%) — *trans*-2-Phenoxycyclopentylamine

(As actually reported, the azide was reduced by hydrogenation over a palladium catalyst, and the amine was isolated as its hydrochloride salt in 66% yield.)

(*d*) Recognition that the primary amine is derivable from the corresponding nitrile by reduction,



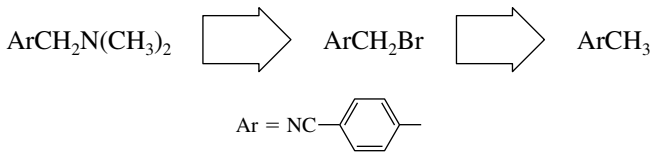
and that the necessary tertiary amine function can be introduced by a nucleophilic substitution reaction between the two given starting materials suggests the following synthesis.



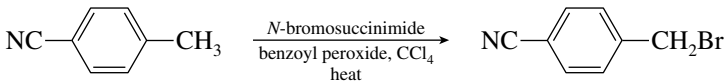
N-Methylbenzylamine — 4-Bromobutanenitrile — *N*-Benzyl-*N*-methyl-1,4-butanediamine

Alkylation of *N*-methylbenzylamine with 4-bromobutanenitrile has been achieved in 92% yield in the presence of potassium carbonate as a weak base to neutralize the hydrogen bromide produced. The nitrile may be reduced with lithium aluminum hydride, as shown in the equation, or by catalytic hydrogenation. Catalytic hydrogenation over platinum gave the desired diamine, isolated as its hydrochloride salt, in 90% yield.

(*e*) The overall transformation may be viewed retrosynthetically as follows:



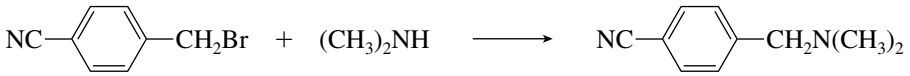
The sequence that presents itself begins with benzylic bromination with *N*-bromosuccinimide.



p-Cyanotoluene — *p*-Cyanobenzyl bromide

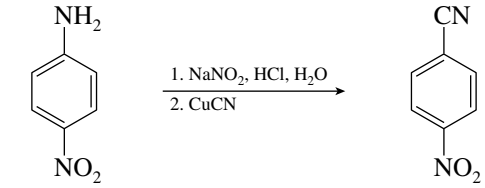
The reaction shown in the equation has been reported in the chemical literature and gave the benzylic bromide in 60% yield.

Treatment of this bromide with dimethylamine gives the desired product. (The isolated yield was 83% by this method.)



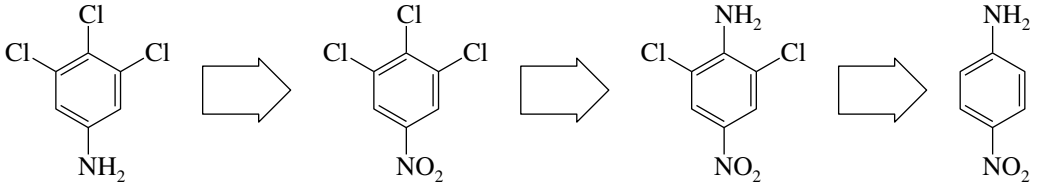
p-Cyanobenzyl bromide Dimethylamine *p*-Cyano-*N*,*N*-dimethylbenzylamine

22.39 (*a*) This problem illustrates the application of the Sandmeyer reaction to the preparation of aryl cyanides. Diazotization of *p*-nitroaniline followed by treatment with copper(I) cyanide converts it to *p*-nitrobenzonitrile.

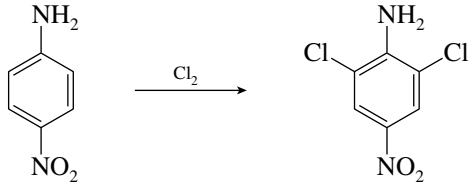


p-Nitroaniline *p*-Nitrobenzonitrile

(*b*) An acceptable pathway becomes apparent when it is realized that the amino group in the product is derived from the nitro group of the starting material. Two chlorines are introduced by electrophilic aromatic substitution, the third by a Sandmeyer reaction.

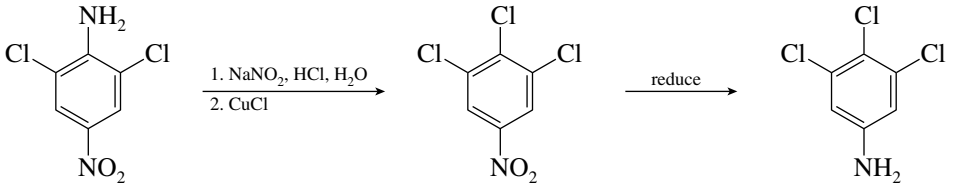


Two of the required chlorine atoms can be introduced by chlorination of the starting material, *p*-nitroaniline.



p-Nitroaniline 2,6-Dichloro-4-nitroaniline

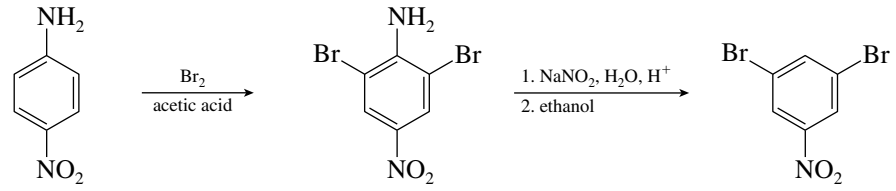
The third chlorine can be introduced via the Sandmeyer reaction. Reduction of the nitro group completes the synthesis of 3,4,5-trichloroaniline.



2,6-Dichloro-4-nitroaniline 1,2,3-Trichloro-5-nitrobenzene 3,4,5-Trichloroaniline

The reduction step has been carried out by hydrogenation with a nickel catalyst in 70% yield.

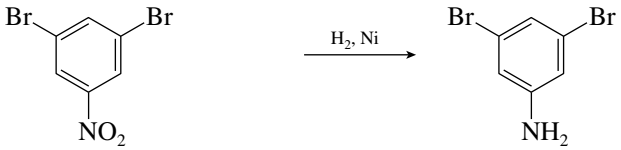
(*c*) The amino group that is present in the starting material facilitates the introduction of the bromine substituents, and is then removed by reductive deamination.



p-Nitroaniline — 2,6-Dibromo-4-nitroaniline (95%) — 1,3-Dibromo-5-nitrobenzene (70%)

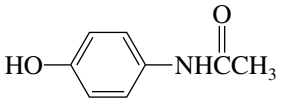
Hypophosphorous acid has also been used successfully in the reductive deamination step.

(*d*) Reduction of the nitro group of the 1,3-dibromo-5-nitrobenzene prepared in the preceding part of this problem gives the desired product. The customary reducing agents used for the reduction of nitroarenes would all be suitable.



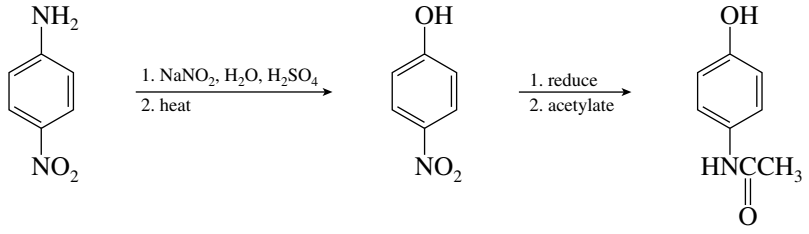
1,3-Dibromo-5-nitrobenzene [prepared from *p*-nitroaniline as in part (*c*)] — 3,5-Dibromoaniline (80%)

(*e*) The synthetic objective is



p-Acetamidophenol

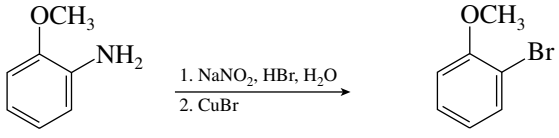
This compound, known as **acetaminophen** and used as an analgesic to reduce fever and relieve minor pain, may be prepared from *p*-nitroaniline by way of *p*-nitrophenol.



p-Nitroaniline — *p*-Nitrophenol — *p*-Acetamidophenol

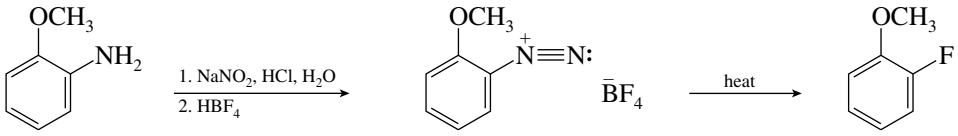
Any of the customary reducing agents suitable for converting aryl nitro groups to arylamines (Fe, HCl; Sn, HCl; H_2, Ni) may be used. Acetylation of *p*-aminophenol may be carried out with acetyl chloride or acetic anhydride. The amino group of *p*-aminophenol is more nucleophilic than the hydroxyl group and is acetylated preferentially.

22.40 (*a*) Replacement of an amino substituent by a bromine is readily achieved by the Sandmeyer reaction.



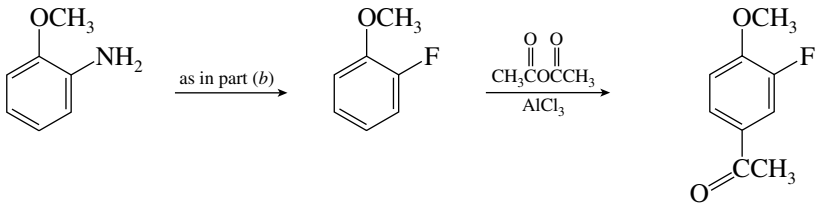
o-Anisidine — *o*-Bromoanisole (88–93%)

(*b*) This conversion demonstrates the replacement of an amino substituent by fluorine via the Schiemann reaction.



o-Anisidine | *o*-Methoxybenzenediazonium fluoroborate (57%) | *o*-Fluoroanisole (53%)

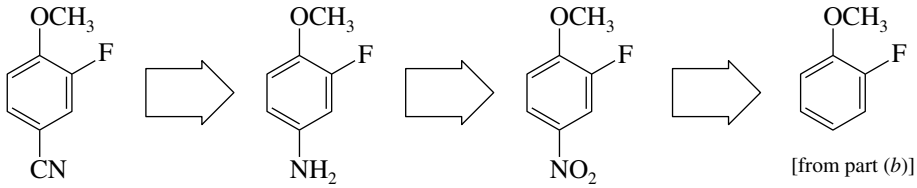
(*c*) We can use the *o*-fluoroanisole prepared in part (*b*) to prepare 3-fluoro-4-methoxyacetophenone by Friedel–Crafts acylation.



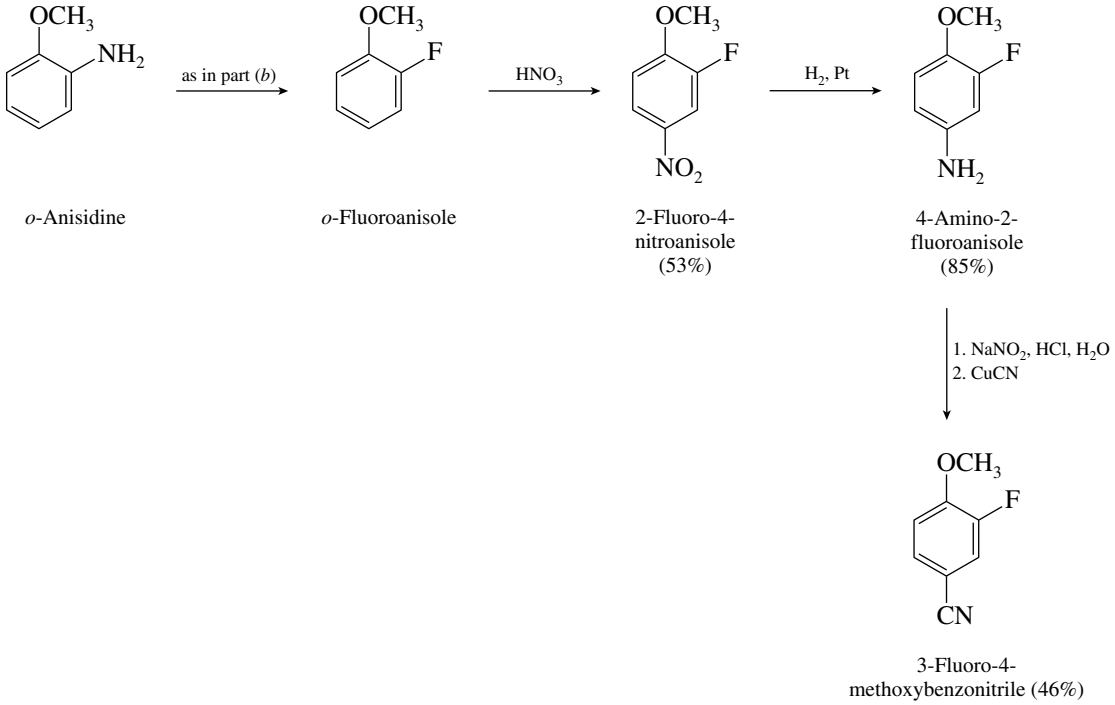
o-Anisidine | *o*-Fluoroanisole | 3-Fluoro-4-methoxyacetophenone (70–80%)

Remember from Section 12.16 that it is the more activating substituent that determines the regioselectivity of electrophilic aromatic substitution when an arene bears two different substituents. Methoxy is a strongly activating substituent; fluorine is slightly deactivating. Friedel–Crafts acylation takes place at the position para to the methoxy group.

(*d*) The *o*-fluoroanisole prepared in part (*b*) serves nicely as a precursor to 3-fluoro-4-methoxybenzonitrile via diazonium salt chemistry.



The desired sequence of reactions to carry out the synthesis is

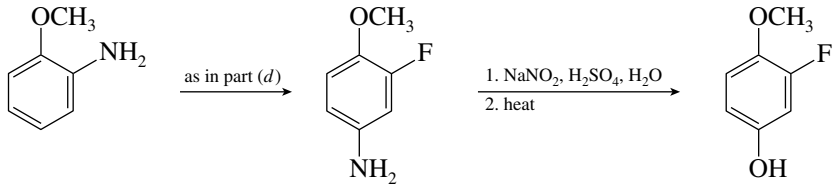


o-Anisidine | *o*-Fluoroanisole | 2-Fluoro-4-nitroanisole (53%) | 4-Amino-2-fluoroanisole (85%)

3-Fluoro-4-methoxybenzonitrile (46%)

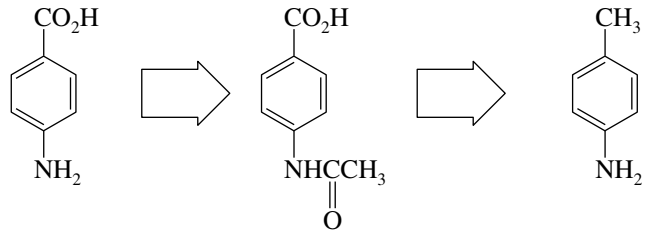
Conversion of *o*-fluoroanisole to 4-amino-2-fluoroanisole proceeds in the conventional way by preparation and reduction of a nitro derivative. Once the necessary arylamine is at hand, it is converted to the nitrile by a Sandmeyer reaction.

(*e*) Diazotization followed by hydrolysis of the 4-amino-2-fluoroanisole prepared as an intermediate in part (*d*) yields the desired phenol.



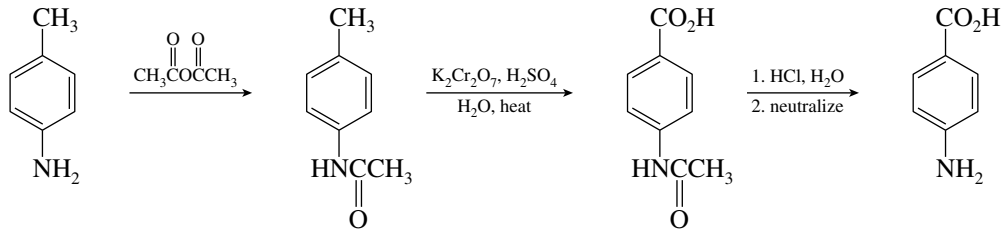
o-Anisidine | 4-Amino-2-fluoroanisole | 3-Fluoro-4-methoxyphenol (70%)

22.41 (*a*) The carboxyl group of *p*-aminobenzoic acid can be derived from the methyl group of *p*-methylaniline by oxidation. First, however, the nitrogen must be acylated so as to protect the ring from oxidation.



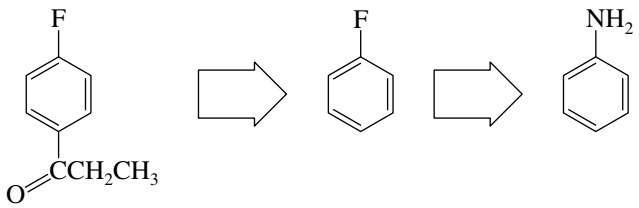
p-Aminobenzoic acid | *p*-Methylaniline

The sequence of reactions to be used is



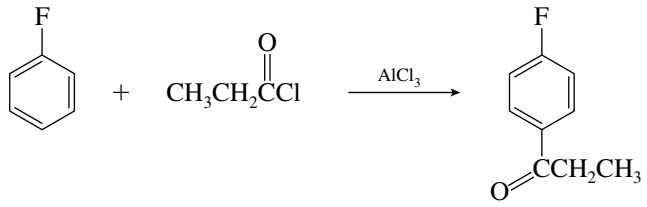
p-Methylaniline | *p*-Methylacetanilide | *p*-Acetamidobenzoic acid | *p*-Aminobenzoic acid

(*b*) Attachment of fluoro and propanoyl groups to a benzene ring is required. The fluorine substituent can be introduced by way of the diazonium tetrafluoroborate, the propanoyl group by way of a Friedel–Crafts acylation. Because the fluorine substituent is ortho, para-directing, introducing it first gives the proper orientation of substituents.



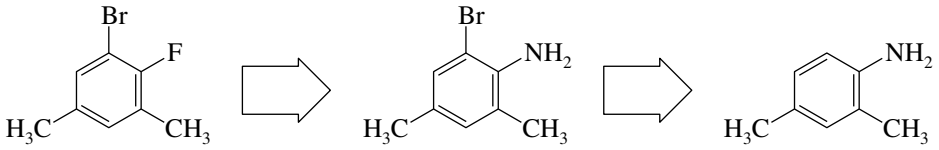
Ethyl *p*-fluorophenyl ketone | Fluorobenzene | Aniline

Fluorobenzene is prepared from aniline by the Schiemann reaction, shown in Section 22.18. Aniline is, of course, prepared from benzene via nitrobenzene. Friedel–Crafts acylation of fluorobenzene has been carried out with the results shown and gives the required ethyl *p*-fluorophenyl ketone as the major product.



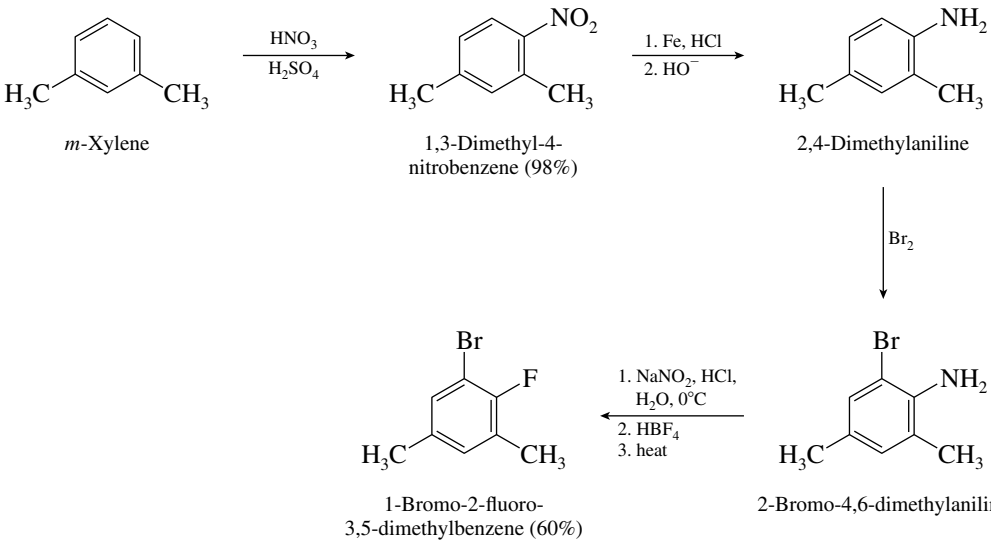
Fluorobenzene | Propanoyl chloride | Ethyl *p*-fluorophenyl ketone (86%)

(*c*) Our synthetic plan is based on the essential step of forming the fluorine derivative from an amine by way of a diazonium salt.



1-Bromo-2-fluoro-3,5-dimethylbenzene | 2,4-Dimethylaniline

The required substituted aniline is derived from *m*-xylene by a standard synthetic sequence.

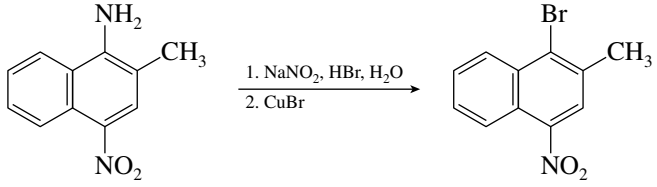


m-Xylene | 1,3-Dimethyl-4-nitrobenzene (98%) | 2,4-Dimethylaniline

1-Bromo-2-fluoro-3,5-dimethylbenzene (60%) | 2-Bromo-4,6-dimethylaniline

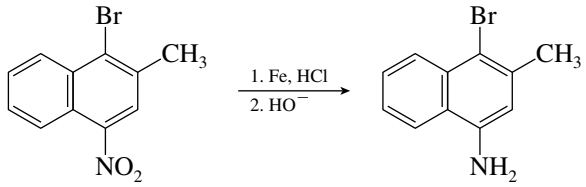
(*d*) In this problem two nitrogen-containing groups of the starting material are each to be replaced by a halogen substituent. The task is sufficiently straightforward that it may be confronted directly.

Replace amino group by bromine:



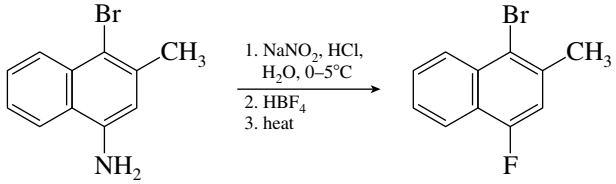
2-Methyl-4-nitro-1-naphthylamine | 1-Bromo-2-methyl-4-nitronaphthalene (82%)

Reduce nitro group to amine:



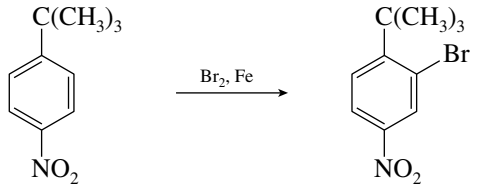
1-Bromo-2-methyl-4-nitronaphthalene → 4-Bromo-3-methyl-1-naphthylamine

Replace amino group by fluorine:



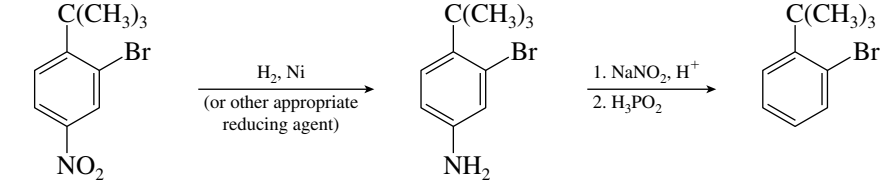
4-Bromo-3-methyl-1-naphthylamine → 1-Bromo-4-fluoro-2-methylnaphthalene (64%)

(*e*) Bromination of the starting material will introduce the bromine substituent at the correct position, that is, ortho to the *tert*-butyl group.



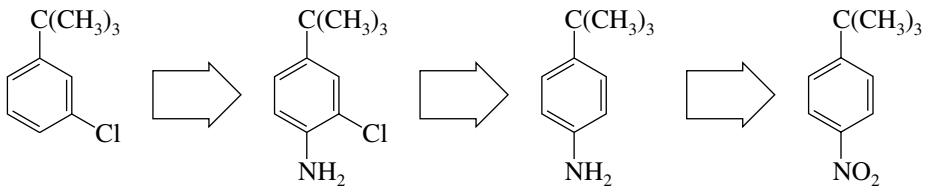
p-tert-Butylnitrobenzene → 2-Bromo-1-*tert*-butyl-4-nitrobenzene

The desired product will be obtained if the nitro group can be removed. This is achieved by its conversion to the corresponding amine, followed by reductive deamination.

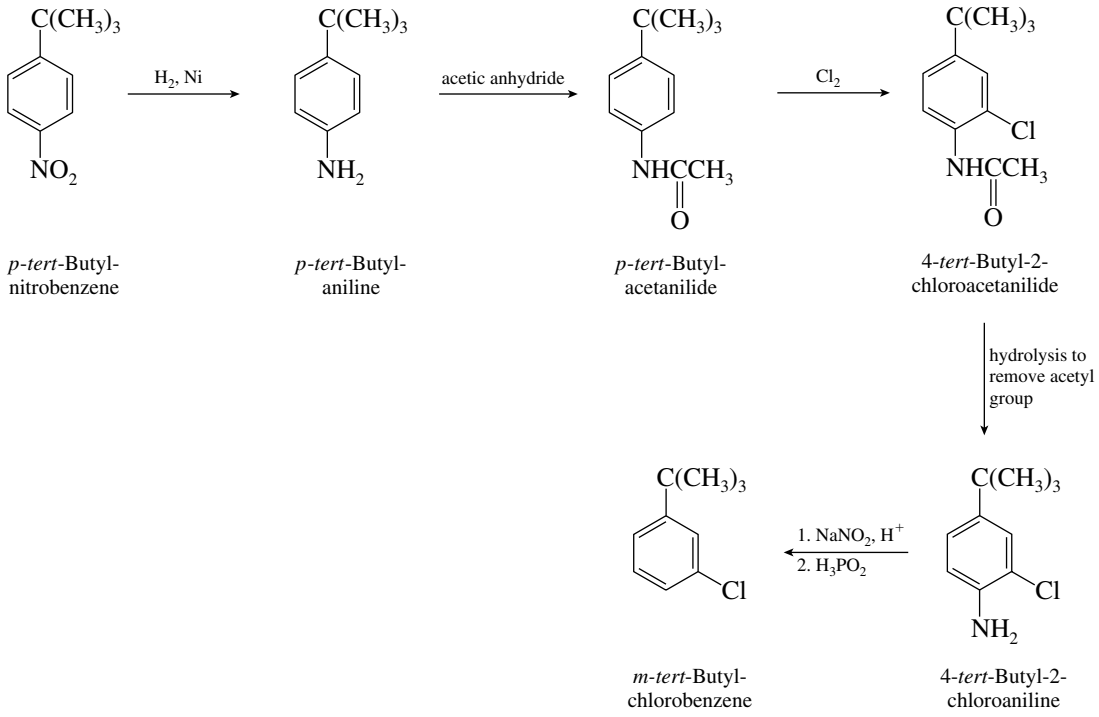


2-Bromo-1-*tert*-butyl-4-nitrobenzene → 3-Bromo-4-*tert*-butylaniline → *o*-Bromo-*tert*-butylbenzene

(*f*) The proper orientation of the chlorine substituent can be achieved only if it is introduced after the nitro group is reduced.

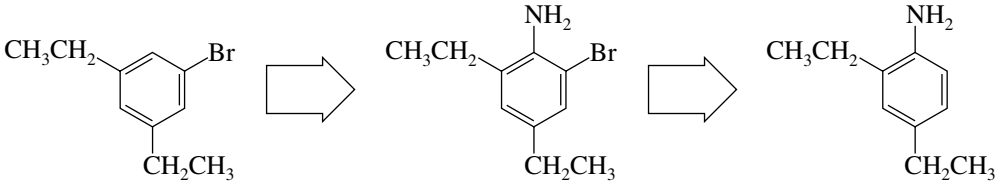


The correct sequence of reactions to carry out this synthesis is shown.



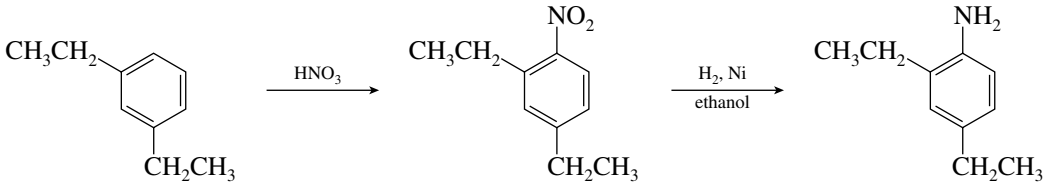
p-tert-Butylnitrobenzene; *p-tert*-Butylaniline; *p-tert*-Butylacetanilide; 4-*tert*-Butyl-2-chloroacetanilide; *m-tert*-Butylchlorobenzene; 4-*tert*-Butyl-2-chloroaniline

(*g*) The orientation of substituents in the target molecule can be achieved by using an amino group to control the regiochemistry of bromination, then removing it by reductive deamination.

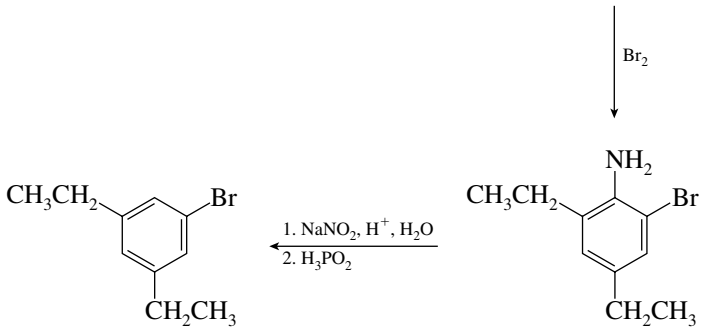


The amino group is introduced in the standard fashion by nitration of an arene followed by reduction.

This analysis leads to the synthesis shown.

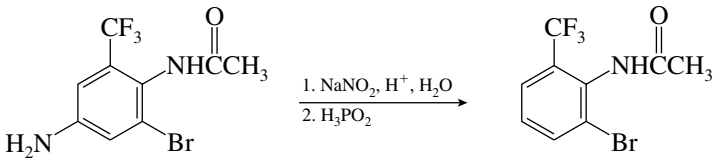


m-Diethylbenzene; 2,4-Diethyl-1-nitrobenzene (75–80%); 2,4-Diethylaniline (80–90%)



1-Bromo-3,5-diethylbenzene (70%); 2-Bromo-4,6-diethylaniline (40%)

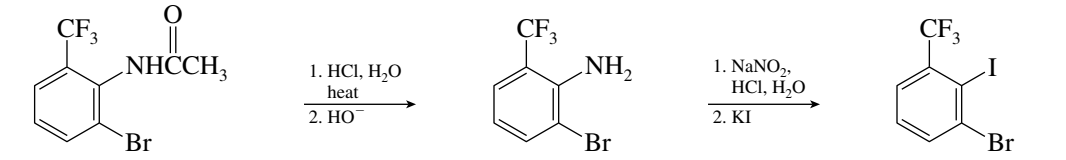
(*h*) In this exercise the two nitrogen substituents are differentiated; one is an amino nitrogen, the other an amide nitrogen. By keeping them differentiated they can be manipulated independently. Remove one amino group completely before deprotecting the other.



4-Amino-2-bromo-6-(trifluoromethyl)acetanilide

2-Bromo-6-(trifluoromethyl)-acetanilide (92%)

Once the acetyl group has been removed by hydrolysis, the molecule is ready for introduction of the iodo substituent by way of a diazonium salt.

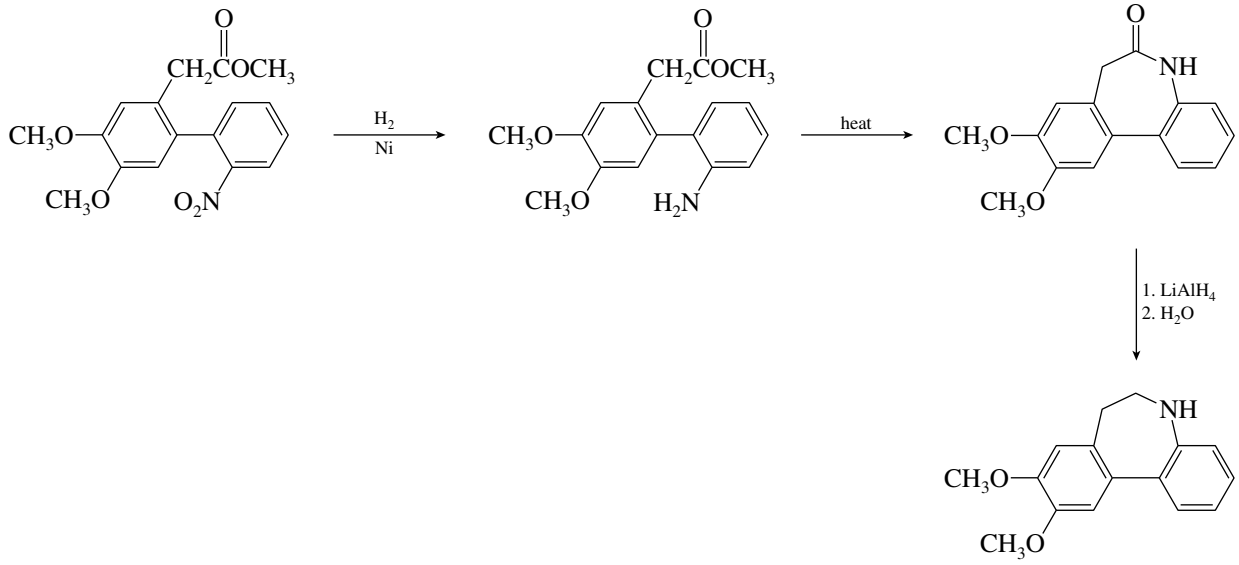


2-Bromo-6-(trifluoromethyl)-acetanilide

2-Bromo-6-(trifluoromethyl)-aniline (69%)

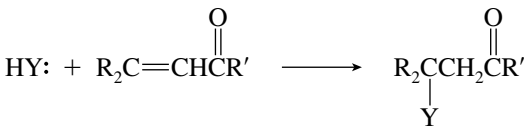
1-Bromo-2-iodo-3-(trifluoromethyl)benzene (87%)

(*i*) To convert the designated starting material to the indicated product, both the nitro group and the ester function must be reduced and a carbon–nitrogen bond must be formed. Converting the starting material to an amide gives the necessary carbon–nitrogen bond and has the advantage that amides can be reduced to amines by lithium aluminum hydride. The amide can be formed intramolecularly by reducing the nitro group to an amine, then heating to cause cyclization.



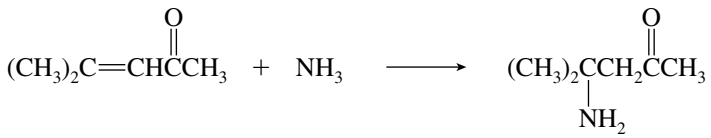
This synthesis is the one described in the chemical literature. Other routes are also possible, but the one shown is short and efficient.

22.42 Weakly basic nucleophiles react with α,β-unsaturated carbonyl compounds by conjugate addition.



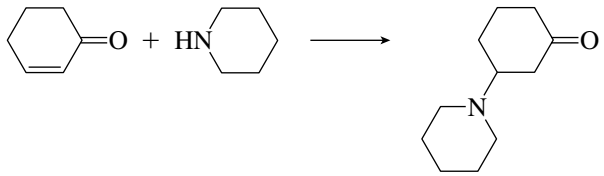
Ammonia and its derivatives are very prone to react in this way; thus conjugate addition provides a method for the preparation of β-amino carbonyl compounds.

(*a*)



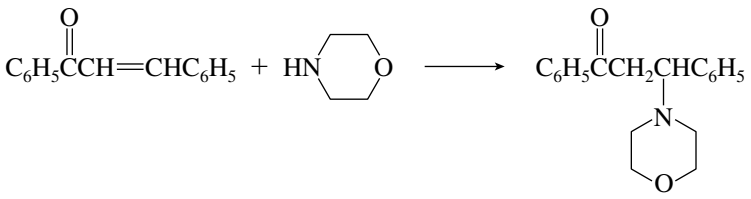
4-Methyl-3-penten-2-one Ammonia 4-Amino-4-methyl-2-pentanone (63–70%)

(*b*)



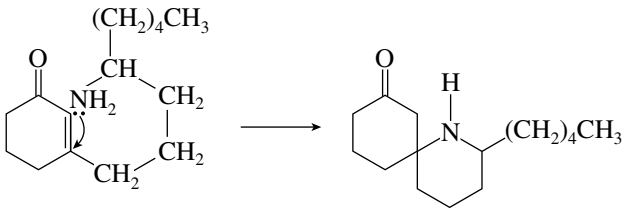
2-Cyclohexenone Piperidine 3-Piperidinocyclo-hexanone (45%)

(*c*)

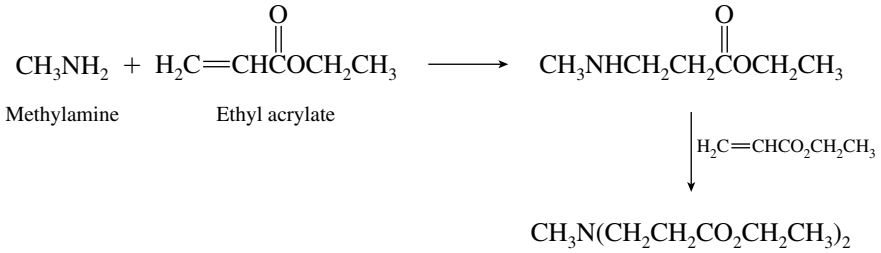


1,3-Diphenyl-2-propen-1-one Morpholine 3-Morpholino-1,3-diphenyl-1-propanone (91%)

(*d*) The conjugate addition reaction that takes place in this case is an intramolecular one and occurs in virtually 100% yield.

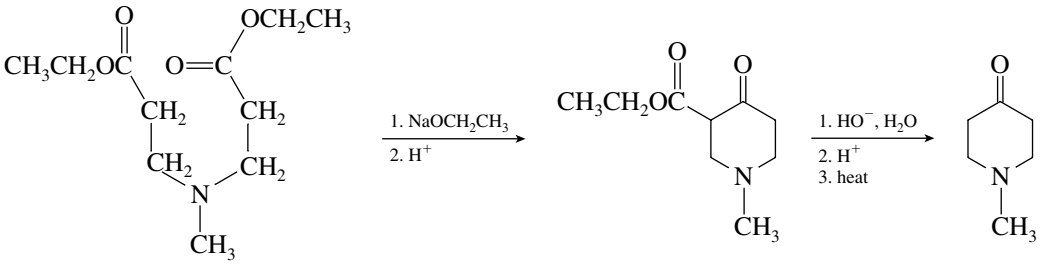


22.43 The first step in the synthesis is the conjugate addition of methylamine to ethyl acrylate. Two sequential Michael addition reactions take place.



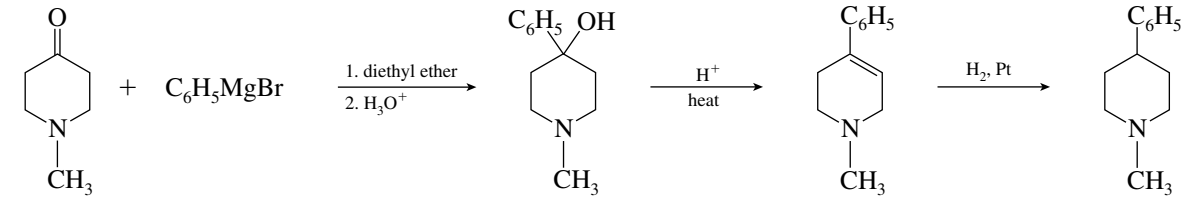
Methylamine Ethyl acrylate

Conversion of this intermediate to the desired *N*-methyl-4-piperidone requires a Dieckmann cyclization followed by decarboxylation of the resulting β-keto ester.



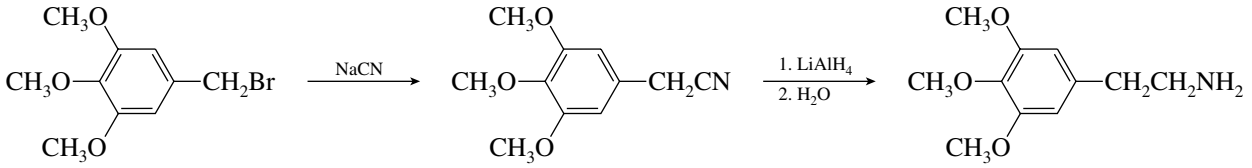
N-Methyl-4-piperidone

Treatment of *N*-methyl-4-piperidone with the Grignard reagent derived from bromobenzene gives a tertiary alcohol that can be dehydrated to an alkene. Hydrogenation of the alkene completes the synthesis.



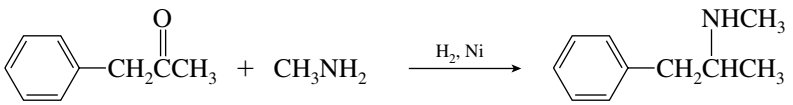
N-Methyl-4-piperidone | Phenylmagnesium bromide | *N*-Methyl-4-phenylpiperidine (compound A)

22.44 Sodium cyanide reacts with alkyl bromides by the S_N2 mechanism. Reduction of the cyano group with lithium aluminum hydride yields a primary amine. This reveals the structure of mescaline to be 2-(3,4,5-trimethoxyphenyl)ethylamine.



3,4,5-Trimethoxybenzyl bromide | 2-(3,4,5-Trimethoxyphenyl)-ethanenitrile | 2-(3,4,5-Trimethoxyphenyl)ethylamine (mescaline)

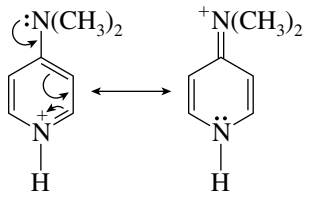
22.45 Reductive amination of a ketone with methylamine yields a secondary amine. Methamphetamine is *N*-methyl-1-phenyl-2-propanamine.



Benzyl methyl ketone | Methylamine | *N*-Methyl-1-phenyl-2-propanamine (methamphetamine)

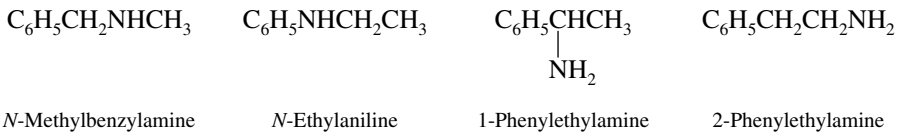
22.46 There is no obvious reason why the dimethylamino group in 4-(*N*,*N*-dimethylamino)pyridine should be appreciably more basic than it is in *N*,*N*-dimethylaniline; it is the ring nitrogen of

4-(*N*,*N*-dimethylamino)pyridine that is more basic. Note that protonation of the ring nitrogen permits delocalization of the dimethylamino lone pair and dispersal of the positive charge.



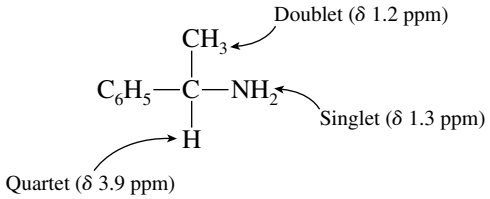
Most stable protonated form of 4-(*N*,*N*-dimethylamino)pyridine

22.47 The ^{1}H NMR spectrum of each isomer shows peaks corresponding to five aromatic protons, so compounds A and B each contain a monosubstituted benzene ring. Only four compounds of molecular formula $C_8H_{11}N$ meet this requirement.

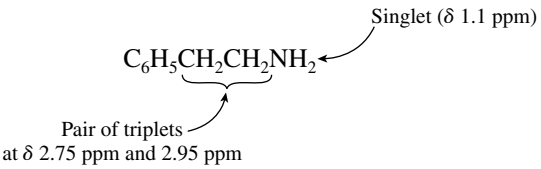


N-Methylbenzylamine | *N*-Ethylaniline | 1-Phenylethylamine | 2-Phenylethylamine

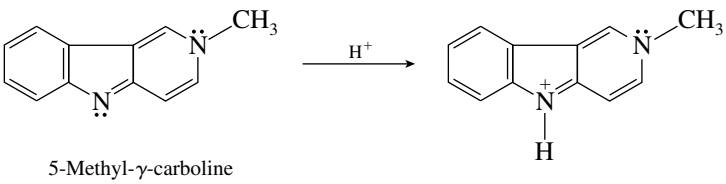
Neither ^{1}H NMR spectrum is consistent with *N*-methylbenzylamine, which would have two singlets due to the methyl and methylene groups. Likewise, the spectra are not consistent with *N*-ethylaniline, which would exhibit the characteristic triplet–quartet pattern of an ethyl group. Although a quartet occurs in the spectrum of compound A, it corresponds to only one proton, not the two that an ethyl group requires. The one-proton quartet in compound A arises from an H—C—CH_3 unit. Compound A is 1-phenylethylamine.



Compound B has an ^{1}H NMR spectrum that fits 2-phenylethylamine.



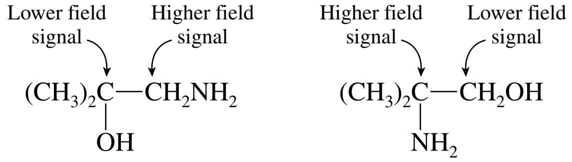
22.48 Only the unshared electron pair on nitrogen that is not part of the π electron cloud of the aromatic system will be available for protonation. Treatment of 5-methyl-γ-carboline with acid will give the salt shown.



5-Methyl-γ-carboline

22.49 Write the structural formulas for the two possible compounds given in the problem and consider how their ^{13}C NMR spectra will differ from each other. Both will exhibit their CH_3 carbons at high field signal, but they differ in the positions of their CH_2 and quaternary carbons. A carbon bonded to

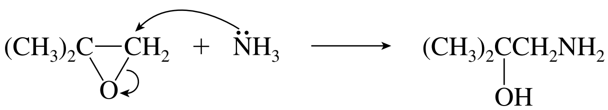
nitrogen is more shielded than one bonded to oxygen, because nitrogen is less electronegative than oxygen.



1-Amino-2-methyl-2-propanol 2-Amino-2-methyl-1-propanol

In one isomer the lowest field signal is a quaternary carbon; in the other it is a CH_2 group. The spectrum shown in Figure 22.10 shows the lowest field signal as a CH_2 group. The compound is therefore 2-amino-2-methyl-1-propanol, $(CH_3)_2\underset{|}{C}CH_2OH$.
NH_2

This compound *cannot* be prepared by reaction of ammonia with an epoxide, because in basic solution nucleophiles attack epoxides at the less hindered carbon, and therefore epoxide ring opening will give 1-amino-2-methyl-2-propanol rather than 2-amino-2-methyl-1-propanol.



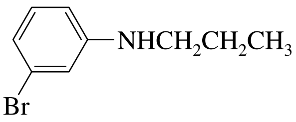
2,2-Dimethyloxirane Ammonia 1-Amino-2-methyl-2-propanol

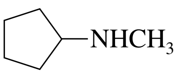
SELF-TEST

PART A

A-1. Give an acceptable name for each of the following. Identify each compound as a primary, secondary, or tertiary amine.

(*a*) $CH_3CH_2C(CH_3)_2NH_2$ (drawn as $CH_3CH_2\overset{CH_3}{\underset{NH_2}{C}}CH_3$)

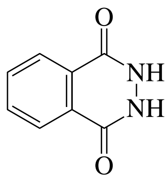
(*c*) 

(*b*) 

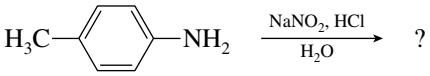
A-2. Provide the correct structure of the reagent omitted from each of the following reactions:

(*a*) $C_6H_5CH_2Br \xrightarrow[\text{2. LiAlH}_4 \quad \text{3. H}_2\text{O}]{\text{1. ?}} C_6H_5CH_2NH_2$

(*b*) $C_6H_5CH_2Br \xrightarrow[\text{2. LiAlH}_4 \quad \text{3. H}_2\text{O}]{\text{1. ?}} C_6H_5CH_2CH_2NH_2$

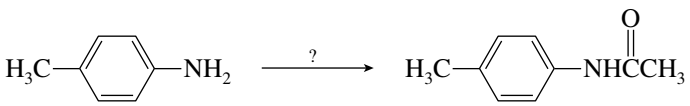
(*c*) $C_6H_5CH_2Br \xrightarrow[\text{2. H}_2\text{NNH}_2]{\text{1. ?}} C_6H_5CH_2NH_2$ + 

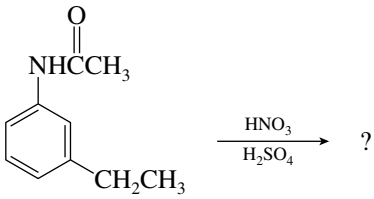
A-3. Provide the missing component (reactant, reagent, or product) for each of the following:

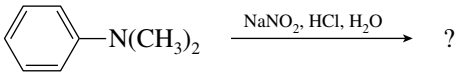
(*a*) 

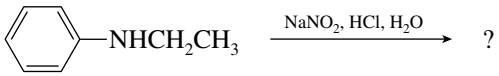
(*b*) Product of part (*a*) $\xrightarrow{CuBr}$?

(*c*) Product of part (*a*) $\xrightarrow{?}$ toluene

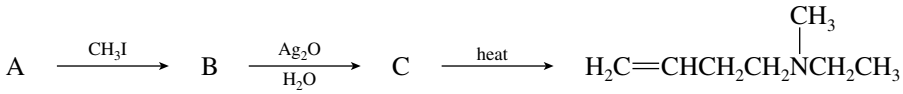
(*d*) 

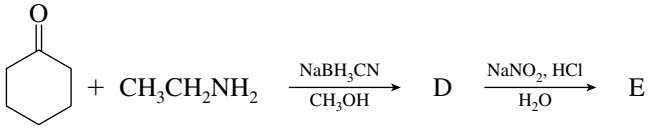
(*e*) 

(*f*) 

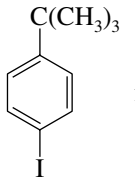
(*g*) 

A-4. Provide structures for compounds A through E in the following reaction sequences:

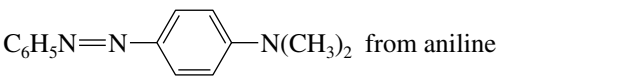
(*a*) 

(*b*) 

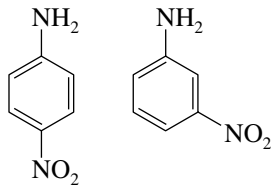
A-5. Give the series of reaction steps involved in the following synthetic conversions:

(*a*)  from benzene

(*b*) *m*-Chloroaniline from benzene

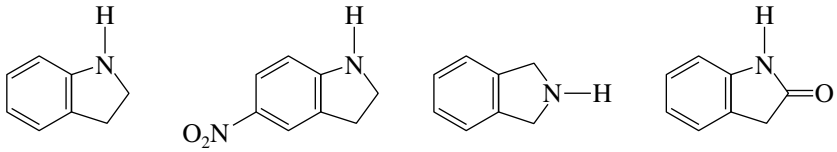
(*c*)  from aniline

A-6. *p*-Nitroaniline (A) is less basic than *m*-nitroaniline (B). Using resonance structures, explain the reason for this difference.



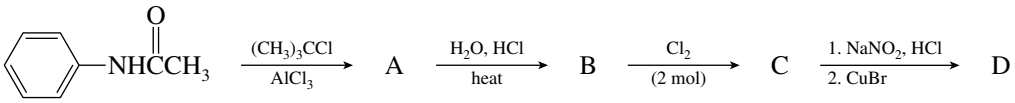
A B

A-7. Identify the strongest and weakest bases among the following:



A B C D

A-8. Write the structures of the compounds A–D formed in the following reaction sequence:

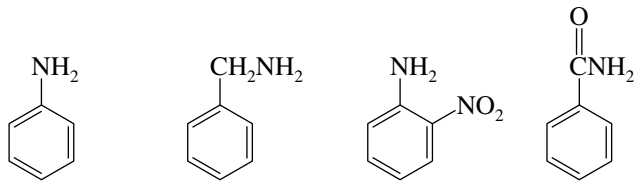


PART B

B-1. Which of the following is a secondary amine?
(*a*) 2-Butanamine
(*b*) *N*-Ethyl-2-pentanamine
(*c*) *N*-Methylpiperidine
(*d*) *N*,*N*-Dimethylcyclohexylamine

B-2. Which of the following C_8H_9NO isomers is the weakest base?
(*a*) *o*-Aminoacetophenone
(*b*) *m*-Aminoacetophenone
(*c*) *p*-Aminoacetophenone
(*d*) Acetanilide

B-3. Rank the following compounds in order of increasing basicity (weakest → strongest):



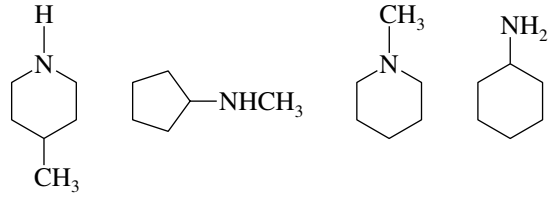
1 2 3 4

(*a*) $4 < 2 < 1 < 3$
(*b*) $4 < 1 < 3 < 2$
(*c*) $4 < 3 < 1 < 2$
(*d*) $2 < 1 < 3 < 4$

B-4. Which of the following arylamines will *not* form a diazonium salt on reaction with sodium nitrite in hydrochloric acid?

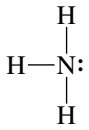
(*a*) *m*-Ethylaniline
(*b*) 4-Chloro-2-nitroaniline
(*c*) *p*-Aminoacetophenone
(*d*) *N*-Ethyl-2-methylaniline

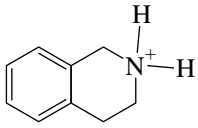
B-5. The amines shown are isomers. Choose the one with the lowest boiling point.

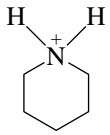


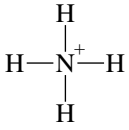
(*a*) (*b*) (*c*) (*d*)

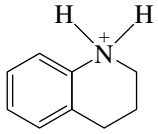
B-6. Which of the following is the strongest acid?

(*a*) 

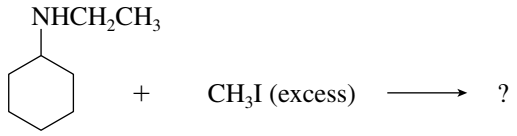
(*b*) 

(*c*) 

(*d*) 

(*e*) 

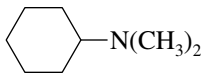
B-7. The reaction

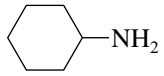


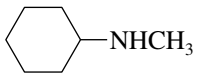
gives as final product

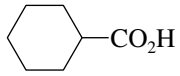
(*a*) A primary amine
(*b*) A secondary amine
(*c*) A tertiary amine
(*d*) A quaternary ammonium salt

B-8. A substance is soluble in dilute aqueous HCl and has a single peak in the region 3200–3500 cm^{-1} in its infrared spectrum. Which of the following best fits the data?

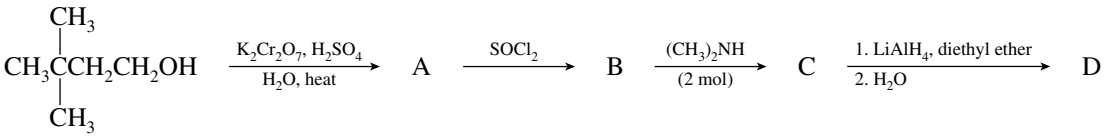
(*a*) 

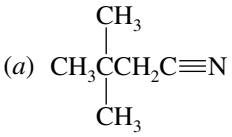
(*b*) 

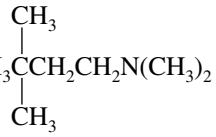
(*c*) 

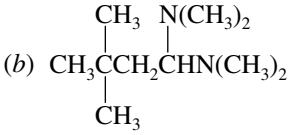
(*d*) 

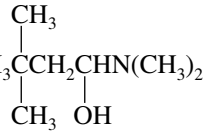
B-9. Identify product D in the following reaction sequence:

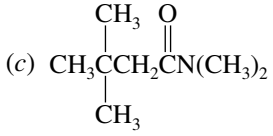


(*a*) 

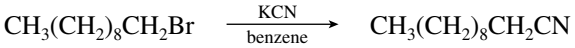
(*d*) 

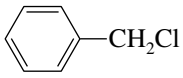
(*b*) 

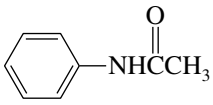
(*e*) 

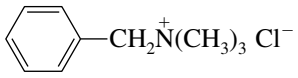
(*c*) 

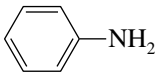
B-10. Which one of the following is the best catalyst for the reaction shown?

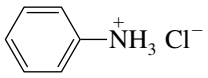


(*a*) 

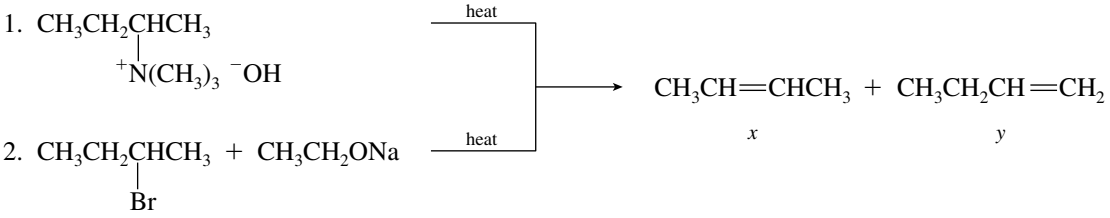
(*c*) 

(*e*) 

(*b*) 

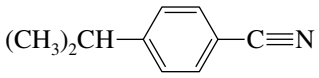
(*d*) 

B-11. What will be the *major* product of each of the two reactions shown?



(*a*) 1*x*, 2*x* (*b*) 1*x*, 2*y* (*c*) 1*y*, 2*x* (*d*) 1*y*, 2*y*

B-12. Which sequence represents the best synthesis of 4-isopropylbenzonitrile?



4-Isopropylbenzonitrile

(*a*) 1. Benzene + $(CH_3)_2CHCl$, $AlCl_3$; 2. Br_2, $FeBr_3$; 3. KCN

(*b*) 1. Benzene + $(CH_3)_2CHCl$, $AlCl_3$; 2. HNO_3, H_2SO_4; 3. Fe, HCl; 4. NaOH; 5. $NaNO_2$, HCl, H_2O; 6. CuCN

(*c*) 1. Benzene + $(CH_3)_2CHCl$, $AlCl_3$; 2. HNO_3, H_2SO_4; 3. Fe, HCl; 4. NaOH; 5. KCN

(*d*) 1. Benzene + HNO_3, H_2SO_4; 2. $(CH_3)_2CHCl$, $AlCl_3$; 3. Fe, HCl; 4. NaOH; 5. $NaNO_2$, HCl, H_2O; 6. CuCN

(*e*) 1. Benzene + HNO_3, H_2SO_4; 2. Fe, HCl; 3. NaOH; 4. $NaNO_2$, HCl, H_2O; 5. CuCN; 6. $(CH_3)_2CHCl$, $AlCl_3$

B-13. The major products from the following sequence of reactions are

$$(CH_3)_2CHCH_2N(CH_2CH_3)_2 \xrightarrow{CH_3I} \xrightarrow[H_2O]{Ag_2O} \xrightarrow{\text{heat}} ?$$

(*a*) $(CH_3)_2CHCH_2NH_2 + H_2C{=}CH_2$

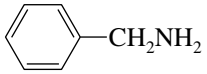
(*b*) $(CH_3)_2NCH_2CH_3 + H_2C{=}C(CH_3)_2$

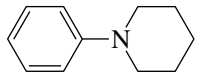
(*c*) $(CH_3)_2CHCH_2\overset{CH_3}{\underset{|}{N}}CH_2CH_3 + H_2C{=}CH_2$

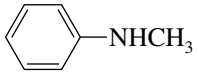
(*d*) $(CH_3)_3\overset{+}{N}CH_2CH_3\ I^- + H_2C{=}CH_2$

(*e*) None of these combinations of products is correct.

B-14. Which compound yields an *N*-nitrosoamine after treatment with nitrous acid ($NaNO_2$, HCl)?

(*a*) 

(*b*) 

(*c*) 

(*d*) 

(*e*)