UNIT 6

FIVE MEMBERED HETEROCYCLES WITH TWO OR MORE HETEROATOMS IN THE RINGS

Structure

6.1 INTRODUCTION

In unit 5, you have learned about the chemistry of benzofused five membered heterocycles with one heteroatom. This is our next unit of this block and we will be discussing here the chemistry of bicyclic heterocyclic compounds containing *two* or *more* heteroatoms.

We will first be explaining the chemistry of benzimidazole .Here, we would list some important compounds containing benzimidazole unit as part of their structure. Then, we will describe the methods of synthesis and the important reactions given by benzimidazole.

Similarly, in the next section, we will be discussing the importance of benzotriazoles. We will describe the methods of synthesis of benzotriazoles and explain the reactions exhibited by them. Finally, in the last section, you will study about the chemistry of *purines.* Purines as you know are very important compounds. In this section, we will be dealing with the synthesis and reactions given by purines.

We hope that the contents of this unit would be very interesting for you to study.

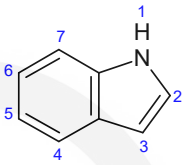
Expected Learning Outcomes

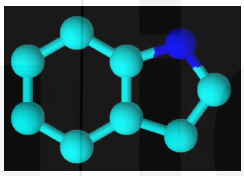
After studying this unit you should be able to:

- ❖ discuss various methods of synthesis of benzimidazoles;
- ❖ explain various chemical reactions given by benzimidazole;
- ❖ describe the methods of of synthesis of benzotriazoles;
- ❖ discuss important reactions exhibited by benzotriazoles;
- ❖ briefly explain various methods of synthesis of purines; and
- ❖ describe important reactions exhibited by purines.

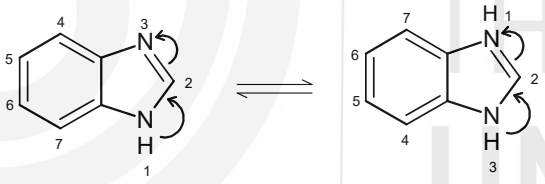
6.2 SYNTHESIS AND REACTIONS OF BENZIMIDAZOLE

Benzimidazole consists of an imidazole nucleus fused with a benzene ring.

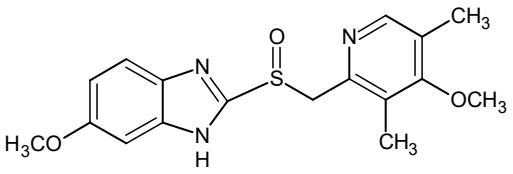




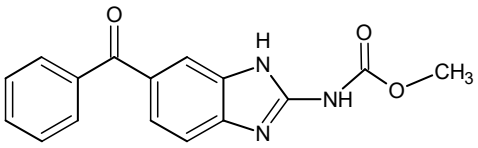
The tautomeric forms of benzimidazole are shown below:



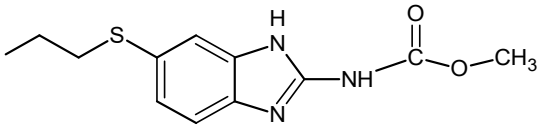
Many benzimidazole based compounds are known to exihibit antimicrobial, antiviral, anticancer, antidiabetic activities. Some important drugs having benzimidazole nucleus include omeprazole, mebendazole, albendazole and bendamuotine.



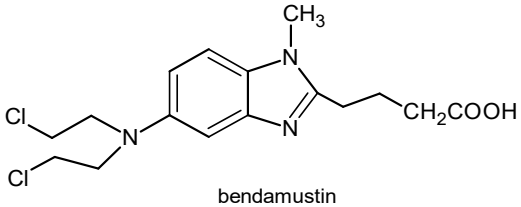
omeprazole



mebendazole



albendazole



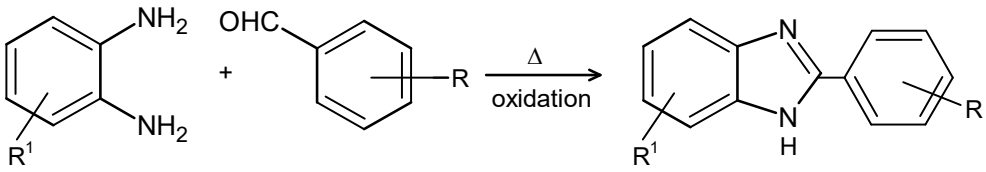
bendamustin

Let us now understand the methods of synthesis of benzimidazoles.

6.2.1 Synthesis of Benzimidazoles

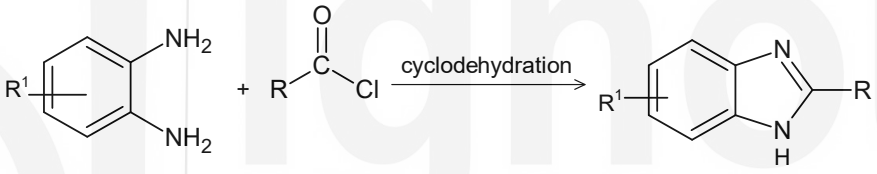
Benzimidazoles can be synthesised by the following methods.

(i) Using *ortho*-phenylenediamine and substituted aldehydes



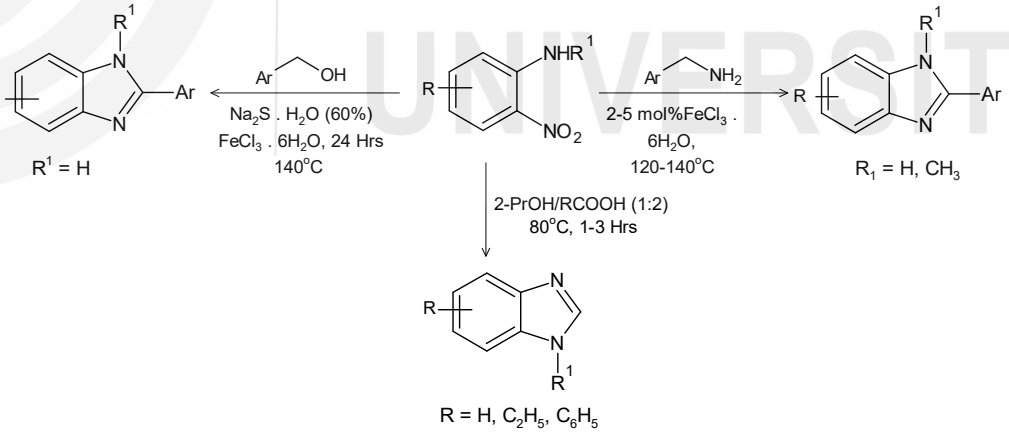
(ii) Reaction of alkyl or aryl or heterocyclic acyl chloride and *ortho*-phenylene diamine

As the reaction of *ortho*-diphenylamine with carboxylic acids gave poor yield of benzimidizole derivatives, the carboxylic acids were converted to acid chlorides which on cyclodehydration using heating with aqueous acids or solvents or other greener methods using glycerol or ionic liquids, gave benzimidazoles.



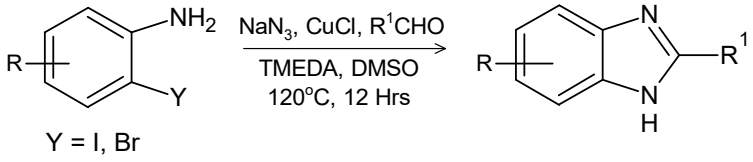
(iii) From *ortho*-nitroarylamines

ortho-nitroarylamines react with substituted alcohols or amines by using reducing agents/redox agents such as $FeCl_3$ to give benzimidazoles.

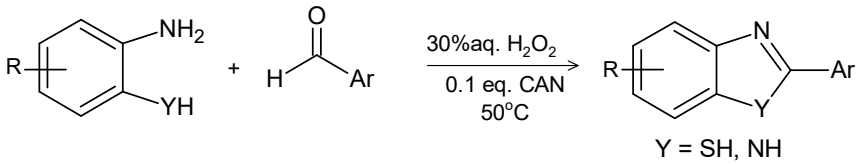


(iv) Using *ortho*-substituted arylamines and aldehydes or ethyl acetoacetate

One pot synthesis such as follows led to benzimidazoles.

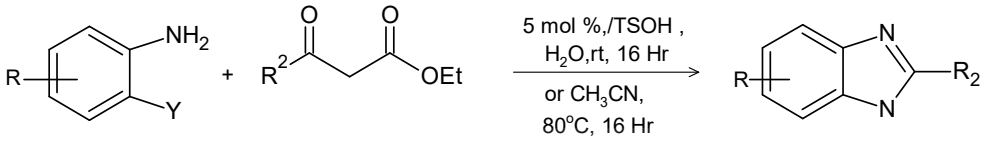


In another variation, Schiff intermediates were obtained from 1,2-diphenylamines/2-meracaptoanilines with aromatic aldehydes which were oxidised using catalytic redox cyclisation involving Ce(IV)/Ce(III)/H_2O_2 to give benzimidazoles.



Y = SH, NH

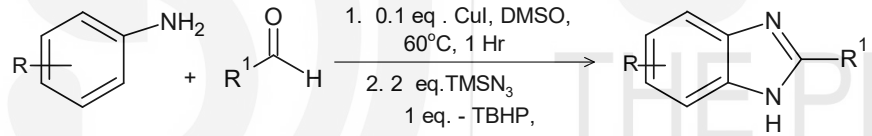
2-Aminoanilines with ethyl acetoacetate on Bronsted acid-catalysed (TsOH) cyclisation using different conditions of oxidants, metals etc. yield benzimidazoles.

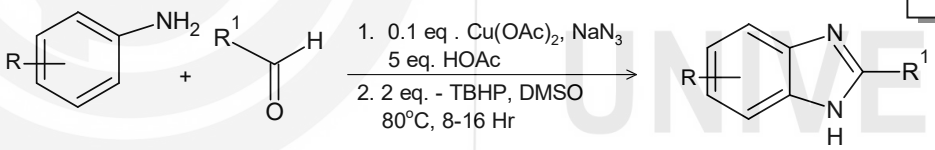


Y = NH, S R^2 = CH_3, C_2H_5, *i*-Pr, C_6H_5

(v) From *N*-aryl amines

A one-pot, multicomponent reaction enables the transformation of commercial aryl amines, aldehydes, and azides into benzimidazole structural units via an efficient copper-catalysed amination of *N*-aryl imines, in which imine acts as a directing group by chelating to the metal centre.





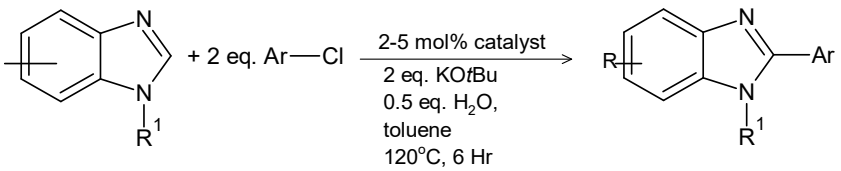
The imine acts as a directing group by chelating to the metal centre.

You will study more about domino reactions in Unit 9.

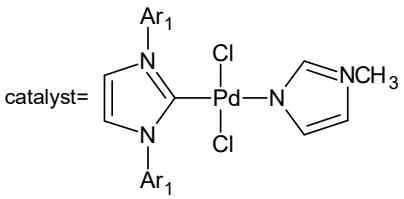
The second reaction involves a *domino* C–H functionalisation, transamination, *ortho*-selective amination and cyclisation.

(vi) Preparation of 2-arylbenzimidazoles

Benzimidazoles can be arylated using suitable aryl chloride in the presence of the catalyst HNC-Pd(II)-Im complex.

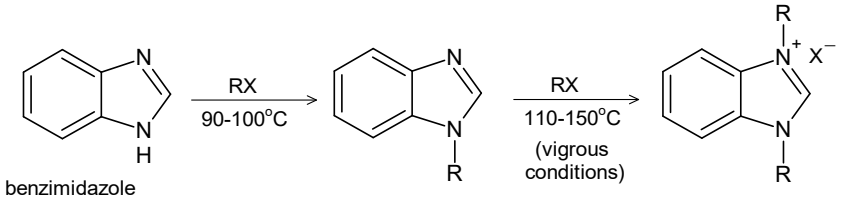


R^1 = CH_3



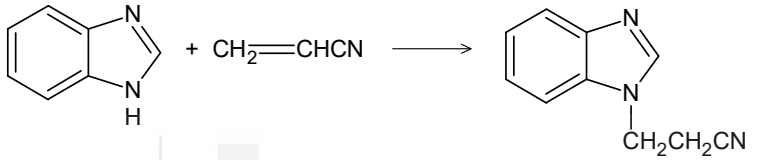
6.2.2 Reactions of Benzimidazole

(i) Both 1-alkyl and 1,3-dialkyl benzimidazoles can be prepared as follows:



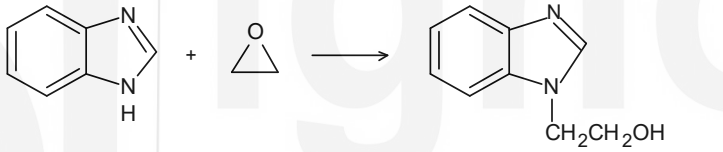
The acylation reaction is also very commonly observed with benzimidazoles upon action of acid chlorides or anhydrides.

(ii) Reaction with acrylonitrile



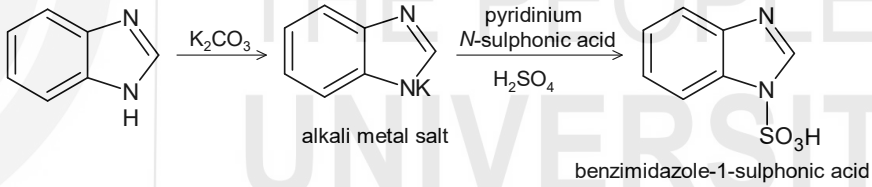
N-cyanoethyl-1*H*-benzimidazole

(iii) Reaction with oxirane



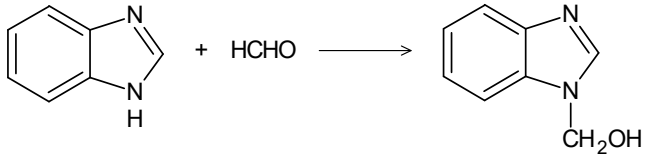
N-(2-hydroxyethyl)-1 *H*-benzimidazole

(iv) Reaction of alkali metal salts of benzimidazole



(v) Reaction with formaldehyde

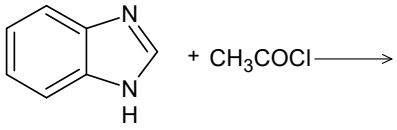
Hydroxymethylbenzimidazole results by the reaction of benzimidazole with formaldehyde.



hydroxymethylbenimidazole

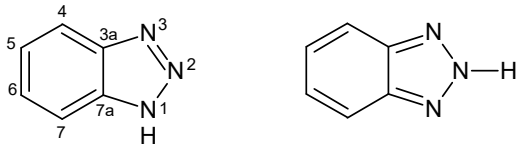
SAQ 1

Predict the product of the following reaction:



6.3 SYNTHESIS AND REACTIONS OF BENZOTRIAZOLE

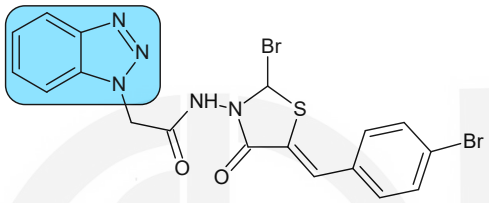
Benzotriazole (BTA) has a ring system with three-nitrogen atoms which is fused with a benzene ring. It shows the following two tautomers:



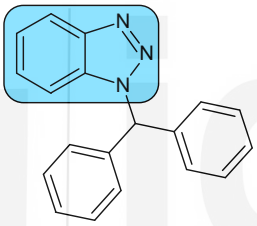
benzotrialzole

1*H*-Benzotriazole 2*H*-Benzotriazole

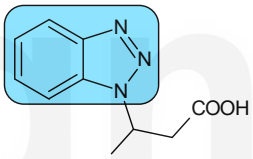
Benzotriazoles exhibit a wide variety of biological activities such as antibacterial, antifungal, antiviral, anti-inflammatory, anti-allergic and antioxidant etc.



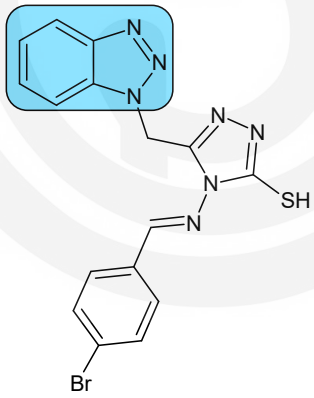
streptomycin equivalent



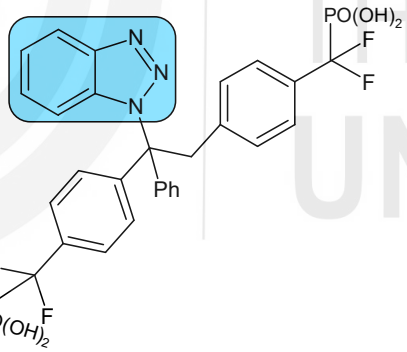
antimicrobial activity



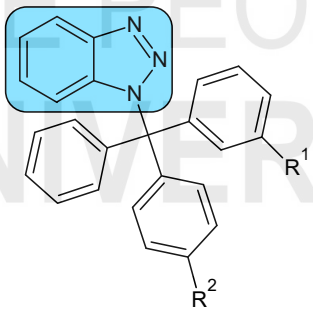
choleretic activity



antimycotic agent

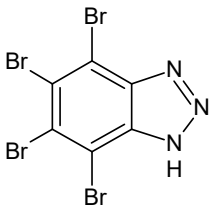


PTB1B inhibitory activity

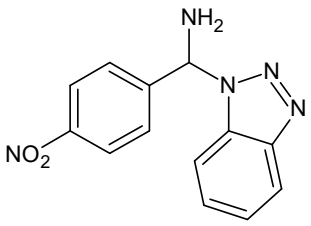


antimycotic activity

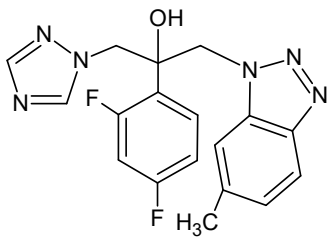
Some more compounds having biological activity are as follows:



anticancer



antibacterial



antifungal

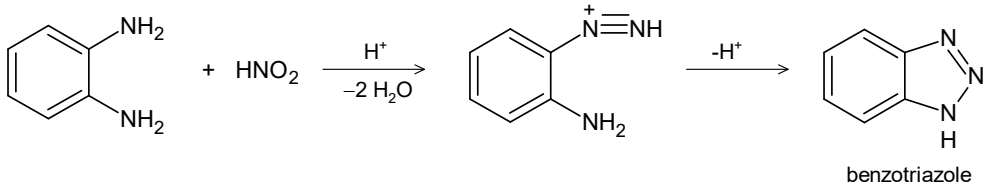
Benzotrialzole can be synthesised by using the following methods.

6.3.1 Synthesis of Benzotrizoles

1. By the reaction of *ortho*-phenylenediamine and nitrous acid

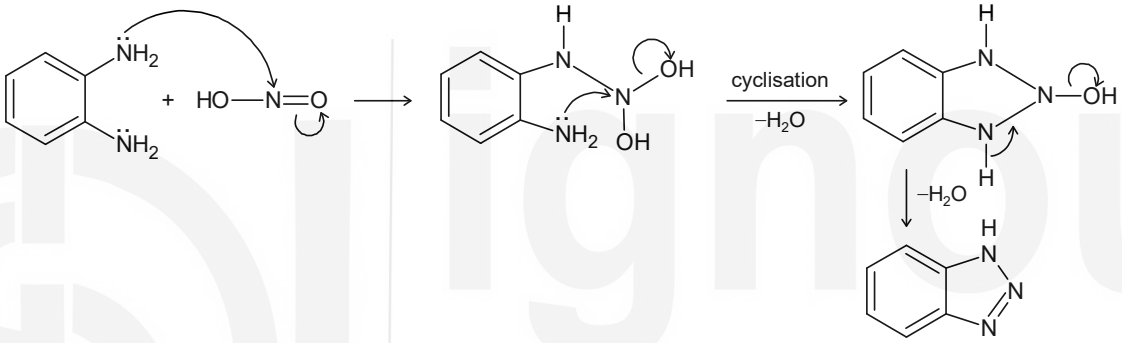
Nitrous acid is obtained by the reaction of sodium nitrite with glacial acetic acid.

$$NaNO_2 + CH_3COOH \longrightarrow HNO_2 + CH_3COONa$$



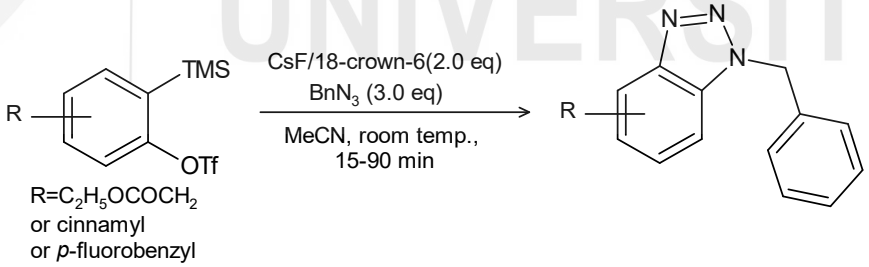
benzotriazole

The mechanism involved in this reaction can be written as follows:



2. 1,3-Dipolar cycloaddition of azides and arynes

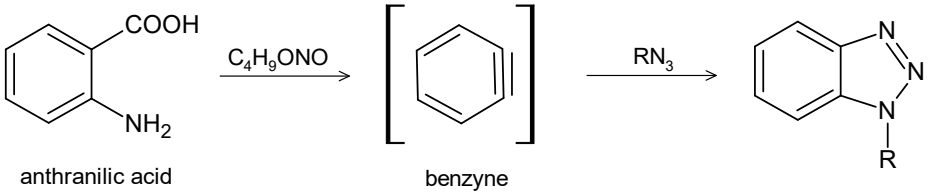
Ortho-elimination of *o*-(trimethylsilyl) aryl triflates by fluoride promoted reaction lead to arynes. These arynes on cycloaddition with azides yield substituted benzotriazoles.



R=$C_2H_5OCOCH_2$
or cinnamyl
or *p*-fluorobenzyl

3. From anthranilic acid

The slow addition of anthranilic acid to an alkyl nitrite yields benzyne *in situ* which yields benzotriazoles on addition of alkyl, acyl, aryl or sulphonyl azides.



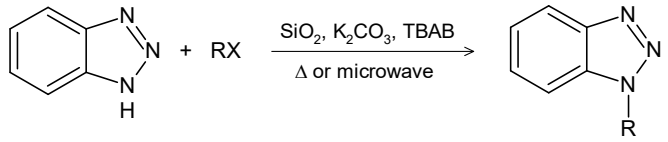
anthranilic acid benzyne

4. *N*-Alkylated benzotriazoles

1*H*-Benzotriazole on methylation with different methylating agents such as methyl sulphate, diazomethane, and methyl halide gives a mixture of 1-methyl- and 2-methylbenzotriazoles in the ratio of 5:17.

Alkylation of 1*H*-benzotriazole with alkyl halide using NaOH or $NaOC_2H_5$ as a base yields 1-alkylbenzotriazole as a major product and 2-alkylbenzotriazole and 1,3-dialkylbenzotriazolium salts as minor products.

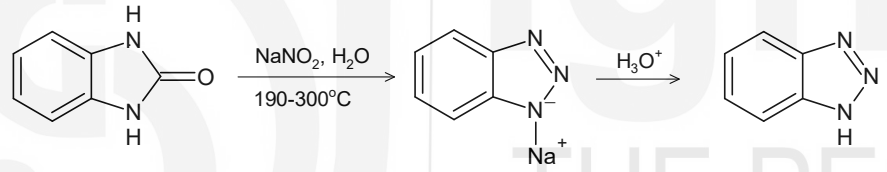
However, 1-alkylbenzotriazoles can be regioselectively prepared as follows:



TBAB = tetrabutylammonium bromide

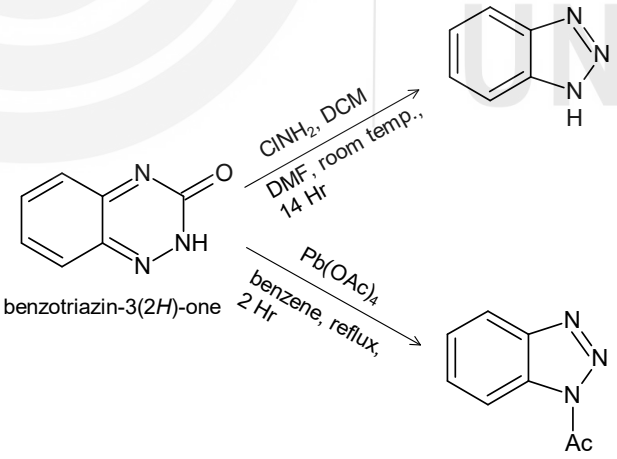
5. From 1,3-dihydrobenzimidazol-2-one

The reaction of 1,3-dihydrobenzimidazol-2-one with sodium nitrite at high temperature and pressure gives sodium salt of benzotriazole which on acidification yields benzotriazole.



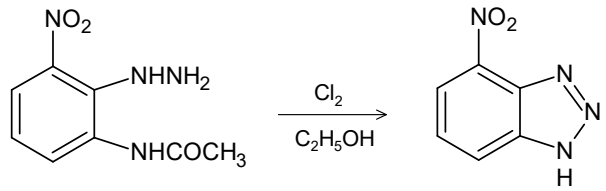
1,3-dihydrobenzimidazole-2-one sodium salt of benzotriazole benzotriazole

6. Ring transformation of benzotriazin-3(2*H*)-one



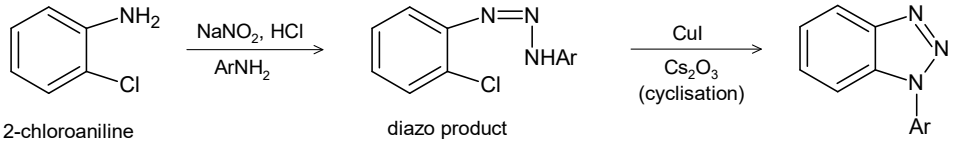
benzotriazin-3(2*H*)-one

7. By oxidative ring closure



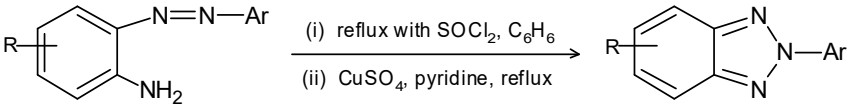
1-acetylamino-2-hydrazino-3-nitrobenzene 4-nitro-1*H*-benzotriazole

8. From 2-chloroaniline

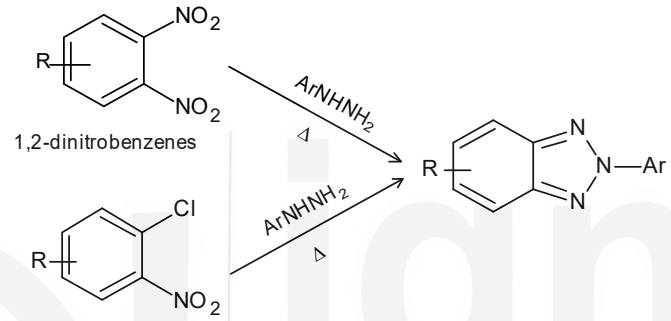


2-chloroaniline diazo product

9. From 2-aminoazobenzenes



10. From nitrobenzenes



1,2-dinitrobenzenes

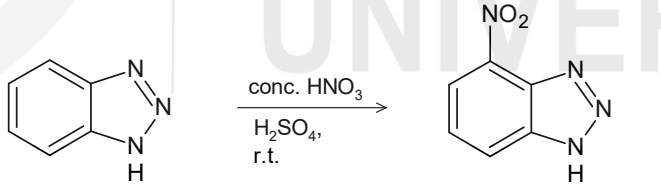
2-nitrochlorobenzenes

6.3.2 Reactions of Benzotriazoles

Benzotriazoles exhibit the following reactions:

1. Nitration

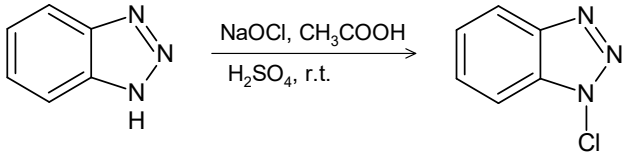
4-Nitro derivative results when benzotriazole is nitrated.



4-nitro-1*H*-benzotriazole

2. Halogenation

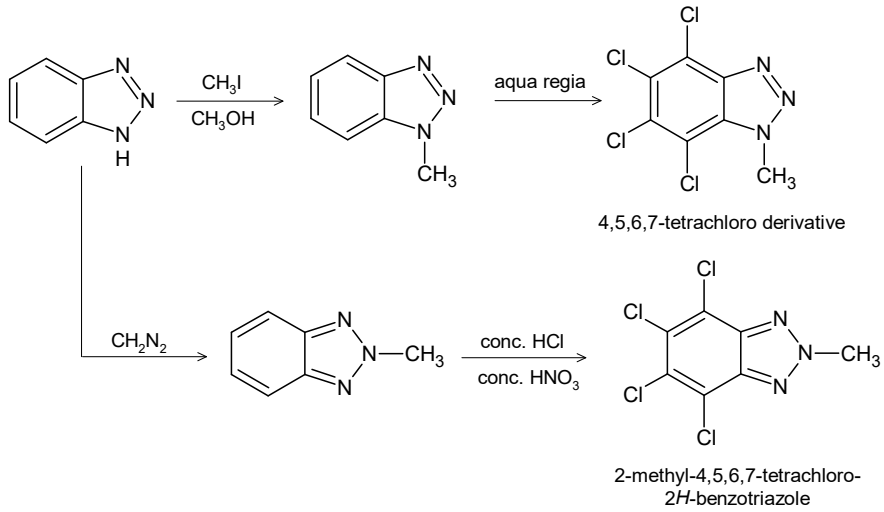
1-Halobenzotriazole is obtained when 1*H*-benzotriazole is reacted with sodium hypohalite in aqueous acetic acid.



SAQ 2

How will you convert benzotriazole to 2-iodobenzotriazole?

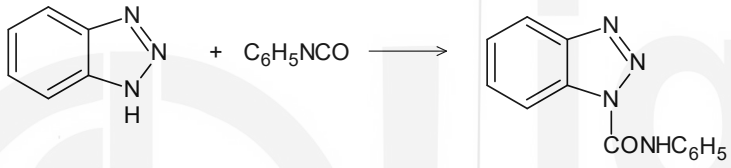
N-Methylated benzotriazoles can be chlorinated as given in the following reactions:



4,5,6,7-tetrachloro derivative

2-methyl-4,5,6,7-tetrachloro-2*H*-benzotriazole

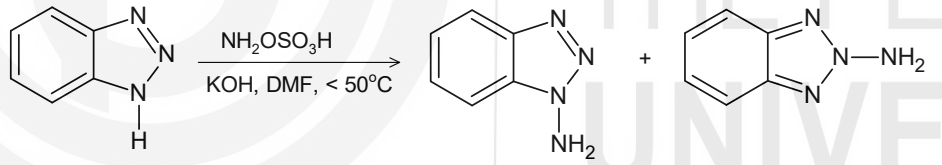
3. Reaction with phenylisocyanate



1-phenylcarbamoylbenzotriazole

4. Amination

A mixture of both the *N*-amino products is obtained on treatment with hydroxylamine-*O*-sulphonic acid in hot aqueous KOH.

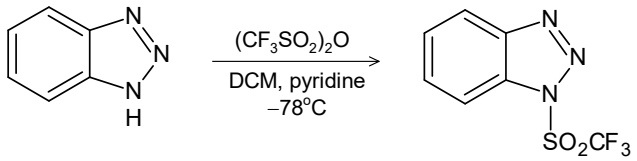


1*H*-benzotriazole-1-amine 2*H*-benzotriazole-2-amine

(3:1)

5. Sulphonation

N-substituted benzotriazole is obtained on reaction with trifluoromethane sulphonic anhydride in dry DCM and dry pyridine.



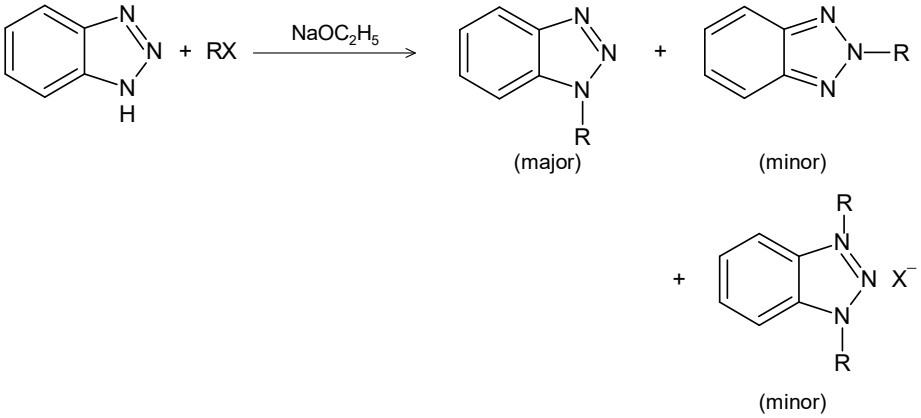
(87%)

1*H*-(trifluoromethyl) sulphonyl-1*H*-benzotriazole

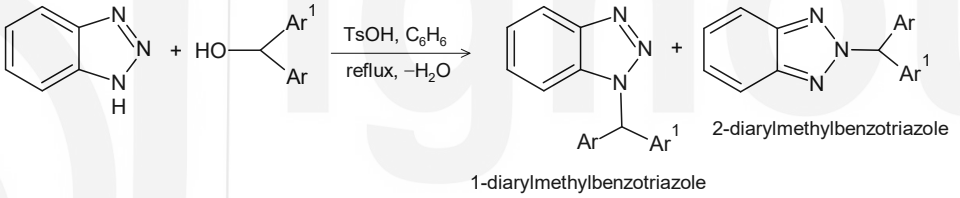
6. Alkylation

A mixture of 1-methyl- and 2-methyl benzotriazoles is obtained when benzotriazole reacts with methyl halide, diazomethane and methyl sulphate.

When an alkyl halide and NaOH or $NaOC_2H_5$ is used, 1-alkyl-benzotriazole is obtained as the major product. However, 2-alkyl- and 1,3-dialkylbenzotriazolium salt are obtained as minor products as shown below.



Let us see what happens when benzotriazole reacts with diarylmethanol using 4-toluenesulphonic acid as the catalyst. We get a mixture of both 1- and 2-substituted products as shown below:



7. Arylation

Activated aryl and heteroaryl halides react with 1*H*-benzotriazole to give 1-arylbenzotriazole. But, in case of 1-chloro-2-nitrobenzene, a mixture of both 1- and 2–substituted products is obtained.

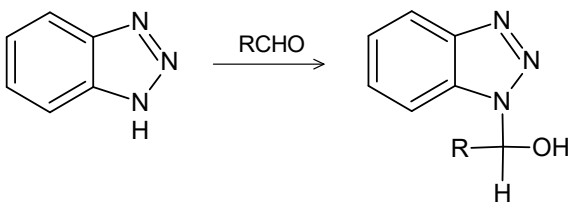
SAQ 3

Can you write the structures of the products formed in the above arylation reaction?

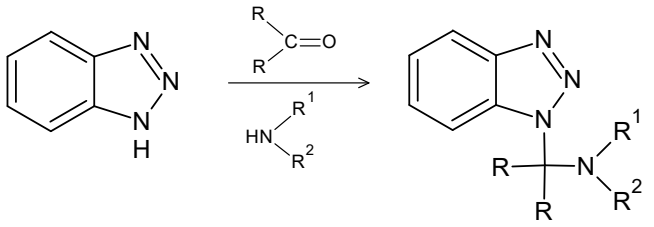
8. Reaction with carbonyl compounds

Different products are obtained with different carbonyl compounds as given below:

(i) With aliphatic aldehydes

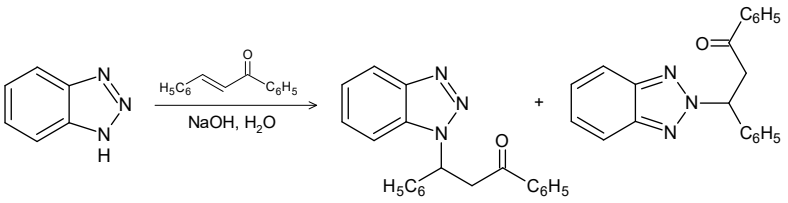


(ii) With ketones in the presence of dialkylamine



1-(dialkylaminoalkyl)-benzotriazole

(iii) With α, β-unsaturated ketones



9. Other uses of benzotriazoles

Benzotriazoles and its derivatives have been widely used as corrosion inhibitors for copper and its alloys in the atmosphere and underwater. It forms a coating or a passive layer over the metal surface.

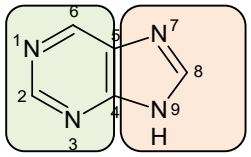
It can also be used in coolants and antifreeze products. It is also used in dishwashing formulations as silver polishing agent.

Besides these uses, benzotriazoles are used in plastics and antifogging agents as UV-light stabilisers.

As benzotriazole is water soluble and does not degrade readily; therefore, it is likely to reach the water bodies despite some treatment at the wastewater plants. It has low toxicity but awareness about its presence as an environmental pollutant is important.

6.4 SYNTHESIS AND REACTIONS OF PURINES

Purine has pyrimidine and imidazole rings fused together as shown below in its structure.



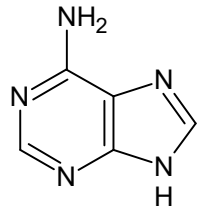
Purine

You can see that first the pyrimidine ring is numbered followed by numbering of imidazole ring.

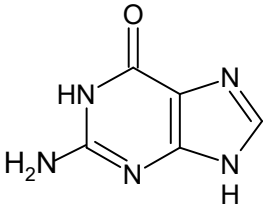
Emil Fischer

The word *purine* was coined by the German chemist Emil Fischer in 1884 from *pure urine*.

Two important purines are adenine and guanine which are the bases present in nucleosides and nucleotides.

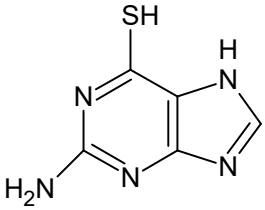


adenine

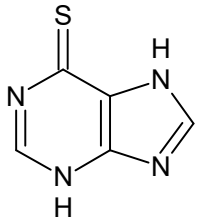


guanine

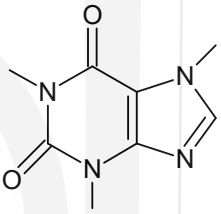
Some purine based molecules of importance are given below.



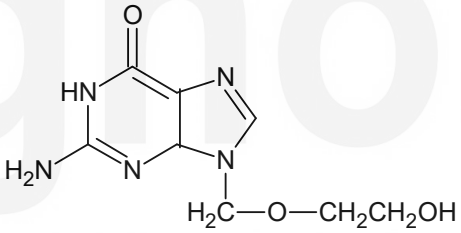
thioguanine
(anticancer)



mercaptopurine
(immunosuppressive
and
anticancer)

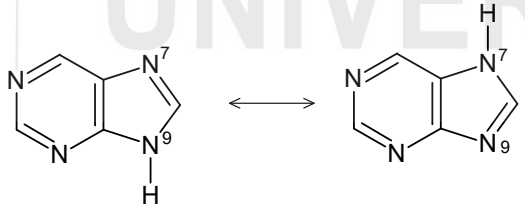


caffeine



acyclovir
(antiviral)

Note that in the structure of purine, four nitrogen atoms are present at positions 1, 3, 7 and 9. Its tautomers can be represented as follows:



9*H*-purine 7*H*-purine

The normal crystalline form of purine has 7*H*-tautomer while the both 9*H*- and 7*H*-tautomers are present in polar solvants.

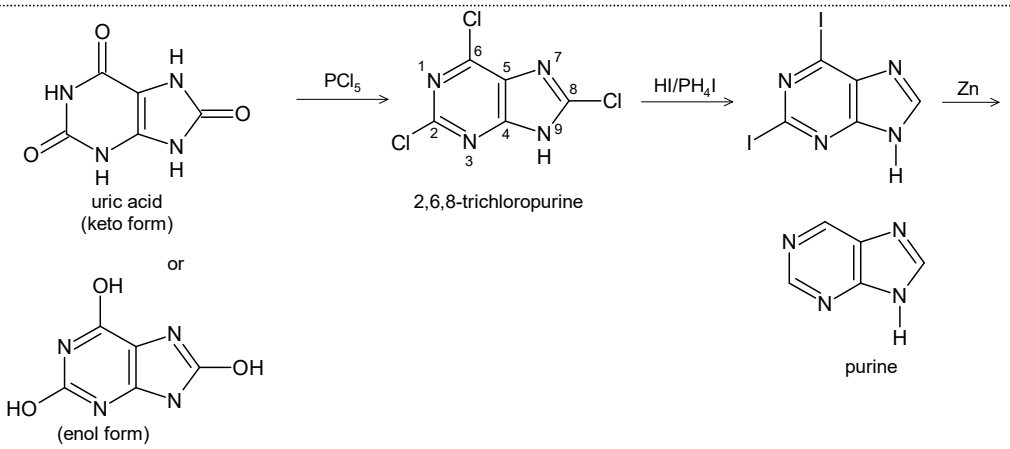
Let us now study the methods of preparation of purine.

6.4.1 Synthesis of Purine

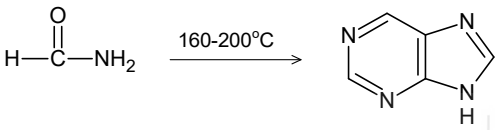
Purine can be synthesised by various methods as discussed below.

1. Fischer synthesis

Emil Fischer synthesised purine in 1998 from uric acid. The scheme of reactions in this synthesis is outlined below:



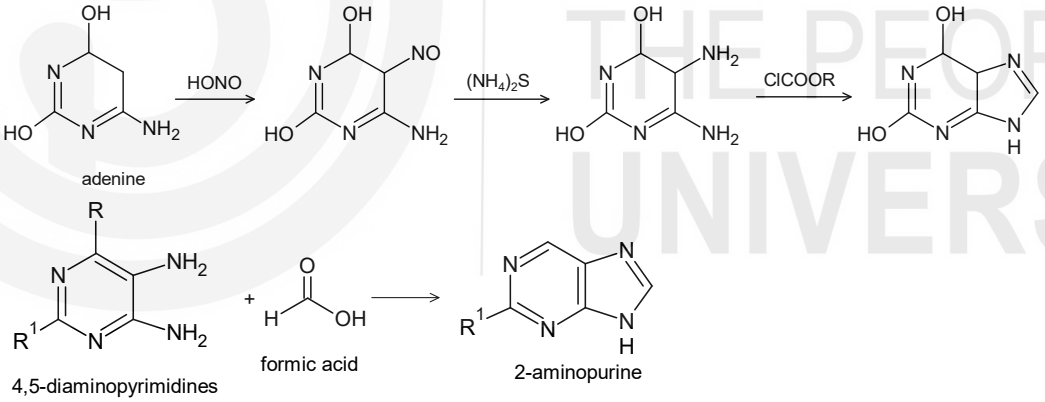
2. By heating fomamide



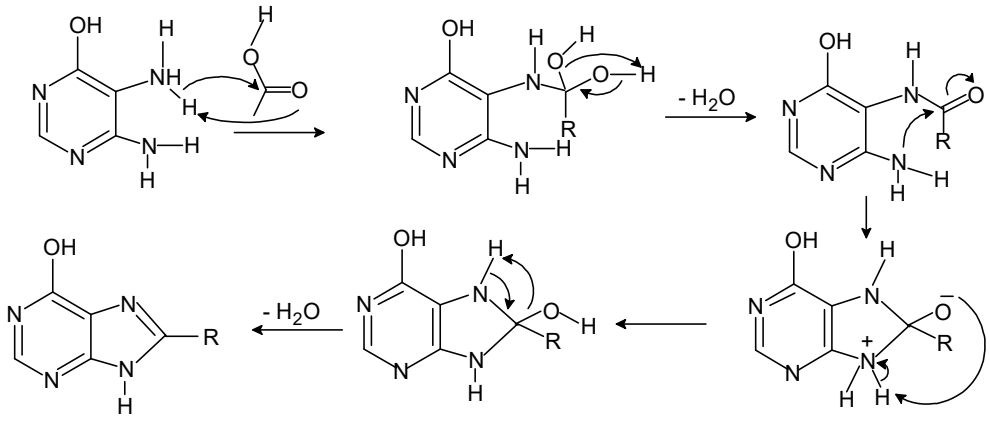
3. Traube's method

This method involves the preparation of 4,5-diaminopyrimidines by introduction of the amino group into the 5-position of 4-amino-6-hydroxy- or 4,6-diaminopyrimidines by nitrosation followed by reduction with ammonium sulphide.

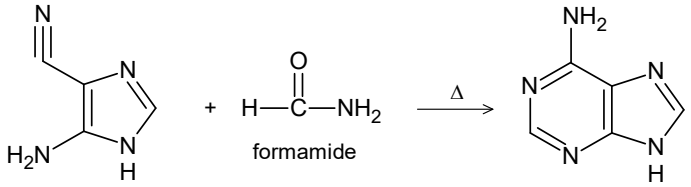
The ring closure is then performed with formic acid or chlorocarbonic ester. The sequence of reactions involved is given below:



The ring closure takes place through the following mechanism.



4. From imidiazoles



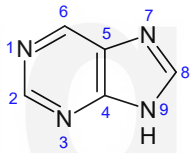
5-amino-1*H*-imidazole-4-carbonitrile

6-aminopurine (adenine)

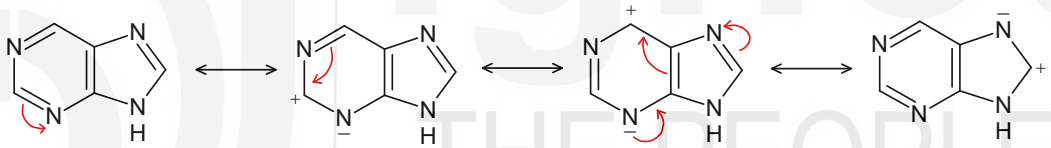
After studying the methods of preparation of purines, let us know what type of reactions the purines undergo.

6.4.2 Reactions of Purine

According to the delocalisation of electrons shown in the following structures, the positions 2, 6, and 8 are susceptible to attack by nucleophiles, whereas the positions 3 and 7 are electron rich, and hence, are susceptible to attack by electrophiles.



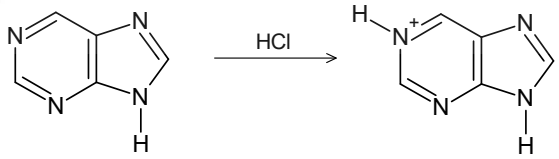
Purine



Let us now understand the reactions of purine.

1. Protonation

Purine, on reaction with acids, involves protonantion at N atom and purinium salts are obtained.

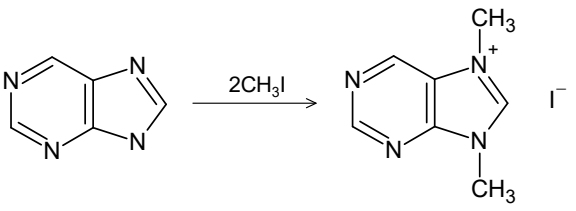


purine

purinium chloride

Since there are four nitrogen atoms, protonation is possible at any of these nitrogens. But, predominant product is by protonation at *N*–1 as shown above.

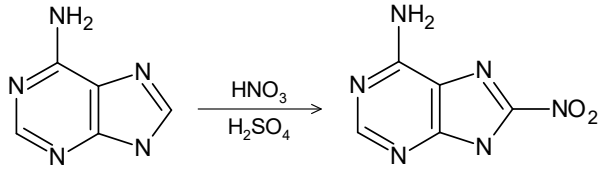
2. Alkylation



7,9-dimethylpurinium iodide

3. Electrophilic Aromatic Substitution

If oxo or amino substituents are present, then electrophilic substitution at 8th position is favoured. For example, adenine gives 8-substituted product as shown below:

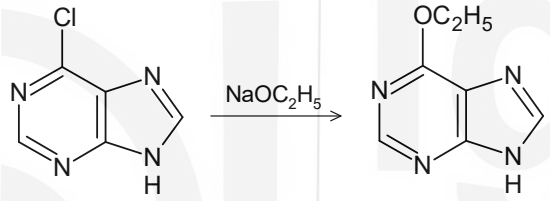


SAQ 4

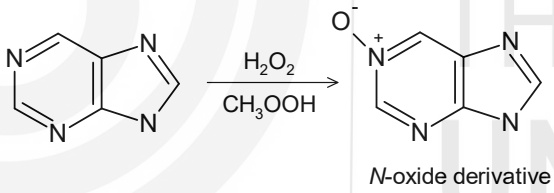
Write the product of reaction of adenine with fuming sulphuric acid.

4. Nucleophilic Substitution Reactions

Purines having halo substituent undergo nucleophilic substitution reactions as the halides are good leaving groups.



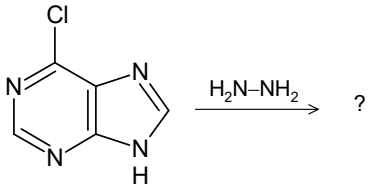
5. *N*-oxide formation



N-oxide derivative

SAQ 5

Write the product when the following reaction takes place.



6.5 SUMMARY

In this unit,you have learnt about the following:

- Synthesis of Benzimidazoles using the following different methods:
  - Using *ortho*-phenylenediamine and substituted aldehydes

- Reaction of alkyl or aryl or heterocyclic acyl chloride and *ortho*-phenylene diamine
- From *ortho*-nitroarylamines
- Using *ortho*-substituted arylamines and aldehydes or ethyl acetoacetate
- From *N*-aryl amines
- Preparation of 2-substituted aryl benzimidazoles

➢ the reactions of benzimidazole with alkyl halides, acrylonitrile oxirane, formaldehyde and sulphonation reaction of its alkali metal salt .

➢ Benzotriazole can be synthesised by using the following methods:

- By the reaction of *ortho*- phenylenediamine and nitrous acid
- 1,3-Dipolar Cycloaddition of azides and arynes
- From anthranilic acid
- From 1,3-dihydrobenzimidazol-2-one
- Ring transformation of benzotriazin-3(2*H*)-one
- By oxidative ring closure
- From 2-chloroaniline, 2-aminoazobenzenes and nitrobenzenes

➢ Benzotriazole exhibited the following reactions: Nitration, halogenation , reaction with phenyl isocyanate, amination, sulphonation, alkylation and arylation. It also exhibited reactions with carbonyl compounds to yield different products.

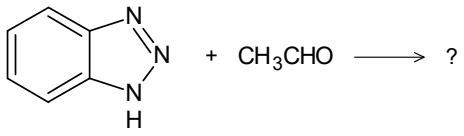
➢ Purines can be synthesised by the following methods:

- Fischer synthesis
- By heating of fomamide
- Traube's method
- From imidiazoles

➢ Purines undergo protonation, alkylation, aromatic electrophilic substitution and nucleophilic substitution reactions.

6.6 TERMINAL QUESTIONS

1. (i) Write the product of the following reaction:



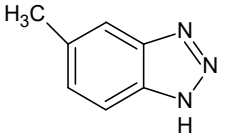
(ii) Which type of reaction it is?

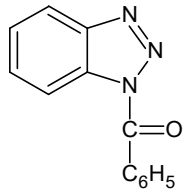
2. What products are obtained when 1*H*-benzotriazole reacts with:

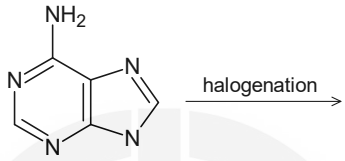
   (i) CH_3COCl

   (ii) CF_3COCl

3. Which starting materials would you use to prepare?

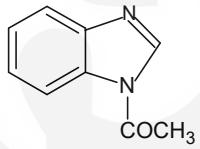
   (i) 

   (ii) 

4. 

6.7 ANSWERS

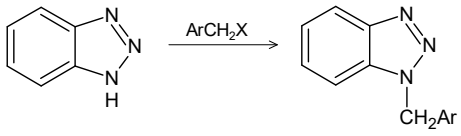
Self Assessment Questions

1. 

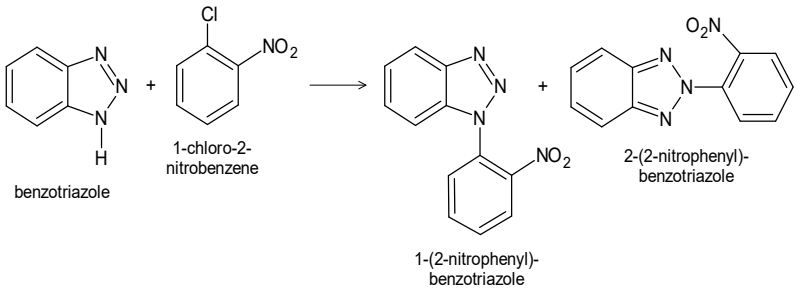
   N-acylbenzimidazole

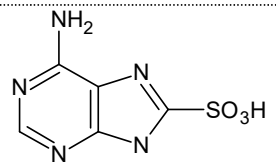
2. Using NaOI, CH_3COOH at room temperature.

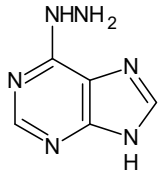
3. A arylation/heteroarylation reaction can be represented as follows:



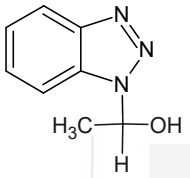
   The reaction involving benzotriazole and 1-chloro-2-nitrobenzene is shown below;



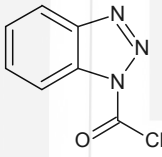
4. 

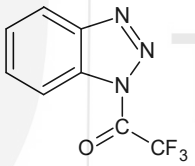
5. 

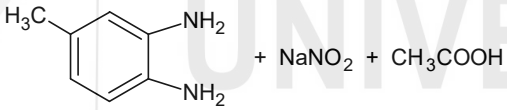
Terminal Questions

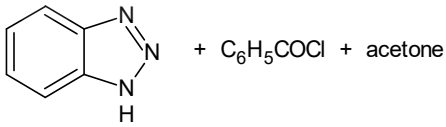
1. (i) 

   (ii) Addition reaction.

2. (i) 

   (ii) 

3. (i) 

   (ii) 

4.