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CHEMISTRY	PAPER No. : 5; Organic Chemistry-II
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CHEMISTRY

PAPER No. : 5; Organic Chemistry-II

MODULE No. : 17; Nucleophilic Substitution at an Allylic, Aliphatic Trigonal and S_Ni Reactions and Nucleophilic Substitution at a Vinylic Carbon, Reactivity Effects of Substrate

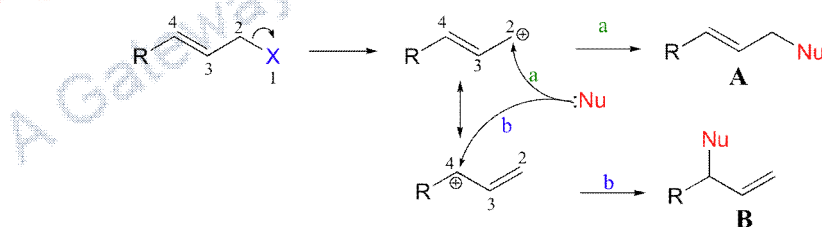
1. Learning Outcomes

After studying this module, you shall be able to

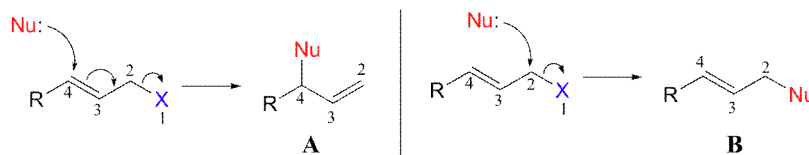
- Know what is an allylic system with orbital π chart
- Learn mechanism of nucleophilic substitution at carbon centre and at aliphatic trigonal centre
- Learn about nucleophilic substitution at vinyl carbon
- Study the S_Ni reaction and evaluate factors affecting the S_Ni reaction
- Analyse rearrangement caused by S_Ni reaction

2. Introduction

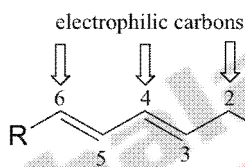
Generally nucleophilic substitution reactions are involved in direct displacement at a carbon center: the carbon that is bonded directly to the leaving group is the target for the attacking nucleophile. This process also known as S_N2 substitution. Generally primary alkyl halides undergo substitution by the S_N2 mechanism and do not undergo S_N1 reaction. However, a primary allyl halide is very reactive in an S_N1 reaction, for example an allyl halide is more than 30 times reactive than an ethyl halide. Allylic substrates are usually accompanied by a rearrangement known as allylic rearrangement. In an S_N1 mechanism, the carbocation intermediate would have two possible resonance forms. This is likely in cases when the allyl compound is unhindered, and a strong nucleophile is used and the products will be similar to those seen with S_N1 substitution. Thus reaction of 1-halo-2-butene system with nucleophile (viz. NaOH) gives a mixture of 2-buten-1-ol and 1-buten-3-ol, as:



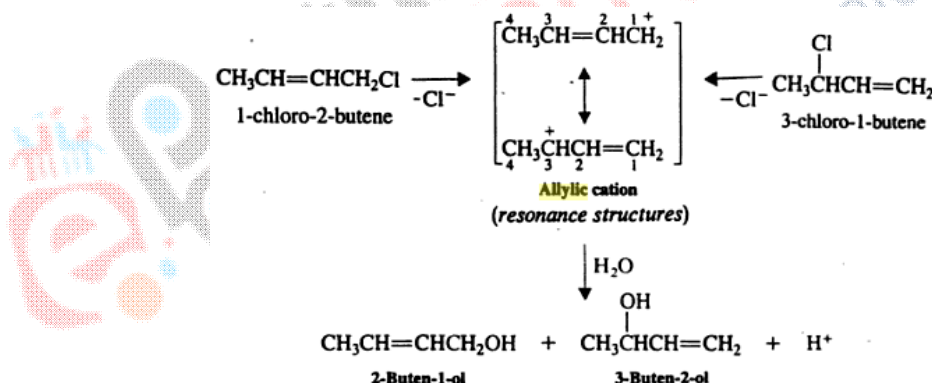
The incoming nucleophile, therefore, could attack either C2 (the carbon originally bonded to the leaving group), or alternatively at C4. These two events would lead to two different substitution products B and A, respectively:



The mechanisms leading to product A are referred to as nucleophilic allylic substitution. They are also sometimes referred to as 1,4 substitutions, according to a numbering system where the leaving group is designated atom. If the conjugated π -orbital system extends further, more allylic substitution products can result: in the following example, 1,6 as well as 1,4 and 1,2 substitutions are possible.



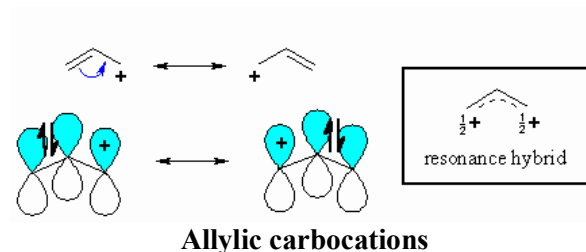
For example: Hydrolysis of 1-Chloro-2-butene



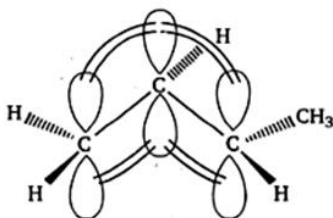
Two distinct mechanisms for aliphatic nucleophilic substitution (S_N) are S_N1 and S_N2 . In terms of stereochemistry, the S_N2 process is attended with inversion of configuration where substitution occurs at a chiral carbon. The S_N1 mechanism involves inversion and retention of configuration (racemization). The question is that arise is whether there are cases where is retention of configuration in S_N reactions. The answer is yes. Besides NGP in S_N reactions, there is another important mechanism labelled S_Ni .

3. Allylic System (orbital π -chart)

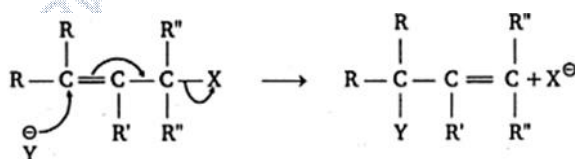
The positions adjacent to $C=C$ often show enhanced reactivity compared to simple alkanes due to the proximity of the adjacent p system. Such positions are referred as "*allylic*". Recall that the term "*vinyllic*" is used to described the atoms directly associated with the $C=C$ unit.



Thus in allylic systems C1 and C3, each carry a partial positive charge and both were attacked by a nucleophile which lead to the formation of two products.

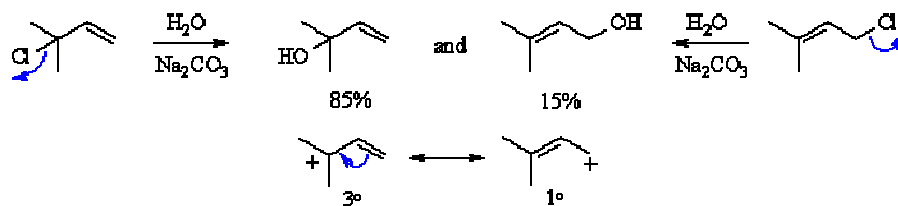


The resonance stabilization of the allylic carbocation is presented as above in the orbital picture. The positive charge is delocalized over two C-atoms by overlap of the filled p-orbital of the π -bond with the vacant p-orbital of the carbocation. Nucleophilic substitution at an allylic carbon can also take place by an S_N2 mechanism in which no allylic rearrangement usually takes place. However, allylic rearrangements can also take place under S_N2 conditions through the following mechanism in which the nucleophile attacks at the γ -carbon rather than the usual position. This mechanism is called S_N2' mechanism. The S_N2' rearrangement normally occurs exclusively when the S_N2 process is sterically hindered.



Thus, the p orbital system of a double bond can stabilize an adjacent carbocation by donating electron density through resonance. Due to the stability of these allylic cations, they are readily formed as intermediates during chemical reactions, for example S_N1 reactions of allylic halides.

- Allyl chlorides, bromides and iodides are good substrates for substitution reactions.
- A variety of nucleophiles can be used to generate a range of new functional groups.
- The process can be complicated by the allylic rearrangement where the nucleophile can attack either of the deficient sites.

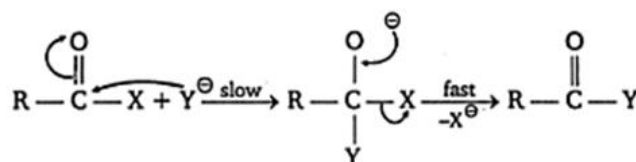


4. Nucleophilic Substitution at Carbon Centre

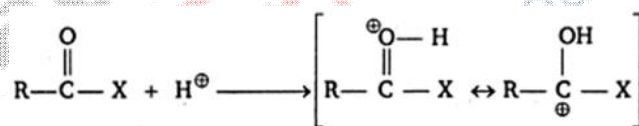
SN	Primary carbon centre	Secondary carbon centre
1.	The π framework of p orbitals provides stabilisation in the transition state. This improves the rate of the S_N2 reaction and also causes the S_N2 reaction to be favoured over S_N1. transition state stabilized by conjugation with the double bond	This subclass of nucleophilic substitution occurs when the nucleophile (HS^-) attacks the alkene instead of the saturated carbon - the S_N2' mechanism. This is due to the saturated carbon being hindered (it is a secondary carbon), making the regular S_N2 mechanism less favorable.
2.	The π framework of p-orbitals provides stabilisation in the transition state. This improves the rate of the S_N2 reaction and also causes the S_N2 reaction to be favoured over S_N1. transition state stabilized by conjugation with the benzene ring	The π framework of p-orbitals provides stabilisation in the transition state. This improves the rate of the S_N2 reaction and also causes the S_N2 reaction to be favoured over S_N1. Another key aspect of this reaction is the change of configuration at the C from S to R. This is because the back side nucleophile attacks of leaving group. inverse of configuration transition state stabilized by conjugation with the benzene ring

5. Nucleophilic Substitution at an Aliphatic Trigonal Carbon

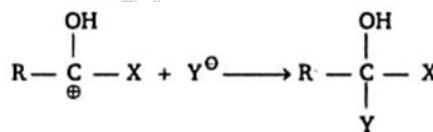
Nucleophilic substitution is also important at trigonal carbons, especially when the carbon is double bonded to an oxygen, sulphur or a nitrogen. The nucleophilic substitution occurs through tetrahedral mechanism, often called as addition-elimination. Although this mechanism displays second order kinetics, it is not the same as the S_N2 mechanism.



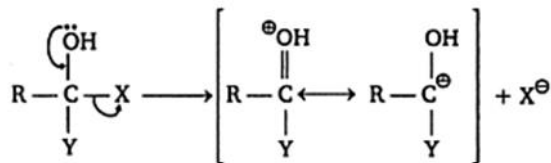
In tetrahedral mechanism first the nucleophile (Y) attacks to give a tetrahedral intermediate containing both X (leaving group) and Y and then the leaving group (X) departs. The tetrahedral mechanism is supported by the second order kinetics and isotopic labelling. In some cases, tetrahedral intermediates have been isolated or detected spectrally. When the reaction is carried out in acid solution the hydrogen ion acts as a catalyst. The reaction rate is increased as it is easier for the nucleophile to attack the carbon when the electron density of it has decreased.



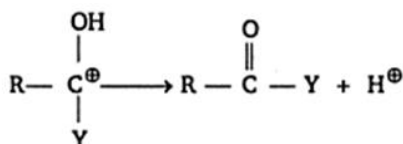
Mechanism: Step 1:



Step 2:

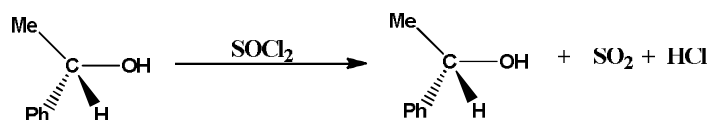


Step 3:



6. S_Ni Reaction

The label S_Ni stands for **substitution, nucleophilic internal**. The reaction between alcohols and thionyl chloride has been studied extensively. A thoroughly studied example is $\text{C}_6\text{H}_5\text{CH}(\text{OH})\text{CH}_3$



It was found that the product chloride is formed with complete retention of configuration on the starting alcohol. The reaction proceeds with the formation of a chlorosulphite ester which collapses with elimination on SO₂. The esters can be isolated. The reaction is common with aryl methanol (ArCH(OH).CH₃) but not with other alcohols.

The chlorosulphite ester could form the product by S_N2 with inversion; S_N1 with racemization. In the present case, there occurs total retention of configuration identity, a new pathway is likely to operate.

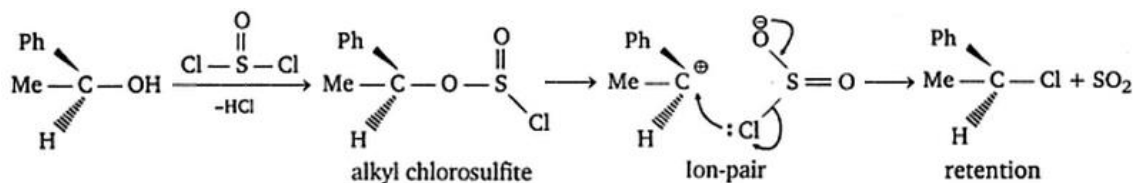
Mechanism of S_Ni

On the basis of experiment facts, the mechanism of S_Ni is formaldehyde as follows.

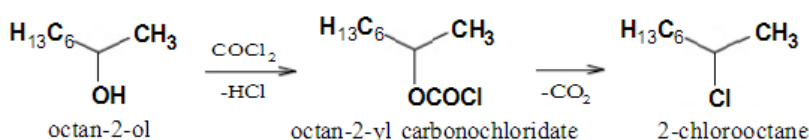
Step-I: The first step is formation of chlorosulphite ester (intermediate)

Step-II: Dissociation of the chlorosulphite ester to form an ion- pair (not dissociated ions)

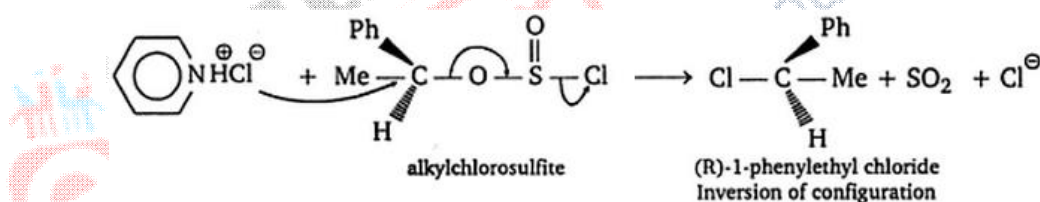
Step-III: Because of the geometry of the ion pair, the chlorine atom is forced to attach the carbonium ion from the same side as original C-O bond of the alcohol (internal attack)



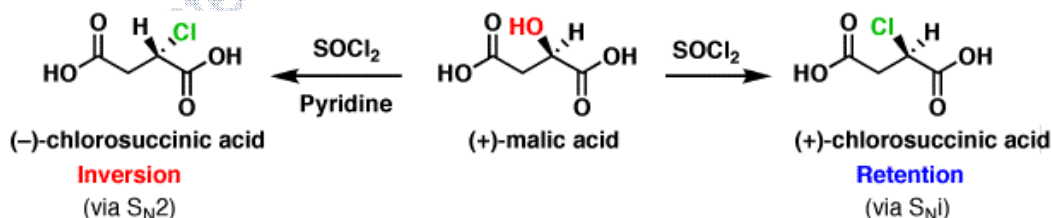
The S_Ni mechanism is occurring rarely and another example being the reaction of 2-octanol with phosgene that proceeds with retention of configuration.



It is interesting to note that if (*S*)-1-phenylethanol and SO_2Cl_2 react in the presence of a tertiary amine such as pyridine, the product (*R*)-1-phenylethylchloride is obtained, i.e. inversion of configuration occurs. The pyridine reacts with HCl , produced in the first step to form pyridinium hydrochloride and the Cl^- being an effective nucleophile, attacks the alkyl chlorosulfite from the back via a normal S_N2 reaction.



Thus we can say in presence of pyridine reaction follow S_N2 reaction mechanism while without pyridine reaction follows S_Ni mechanism. Another example of S_Ni is that of (+) malic acid.



6.1 Rate of reaction

In S_Ni reaction both the reactants are the crucial component and both are playing crucial role in completion of reaction. Thus the rate will be directly proportional to the reactant and catalyst

therefore; we can say the reaction follows a second order rate equation. For example rate equation in case of chlorination using thionyl chloride comes to the following form:

$$\text{Rate} = k [\text{ROH}] [\text{SOCl}_2]$$

Note that the rate of decomposition of the intermediate chlorosulphite ester increases with increases with increase in the polarity of solvent.

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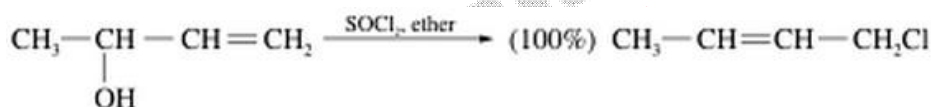
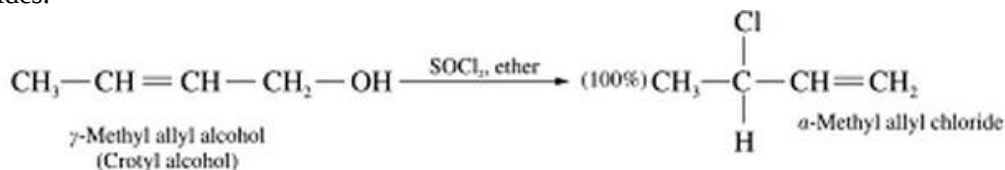
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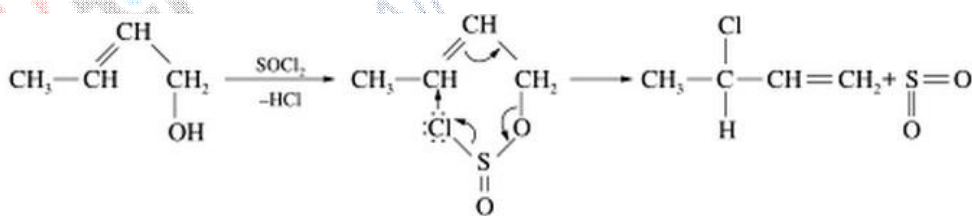
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7. Rearrangement by S_Ni Mechanism

The substituted allyl alcohols react with SOCl_2 in the medium of ether and form substituted allyl chlorides.



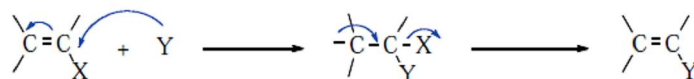
It is interesting to note that the primary isomer principally gives the secondary chloride while the secondary isomer principally the primary chloride. Ordinary allylic rearrangements S_N1 or S_N2 could not be expected to give 100% isomer in both the cases and the mechanism may be explained by S_Ni type of reaction in which a 6-membered chlorosulphinic ester is supposed to be formed. The halogen atom binds itself to the γ -C atom of the allyl alcohol accompanied by simultaneously shift of the double bond and elimination of a molecule of SO_2 .



This type of reaction is called internal substitution with allylic rearrangement, abbreviated as S_Ni , and appears to be the favoured reaction path with allyl chlorosulphites.

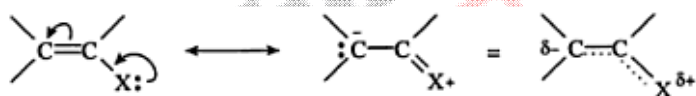
8. Nucleophilic substitution at Vinyl carbon

The subject matter under the title is concerned with nucleophilic substitution at unsaturated carbon such as vinylchloride ($\text{CH}_2=\text{CHCl}$).

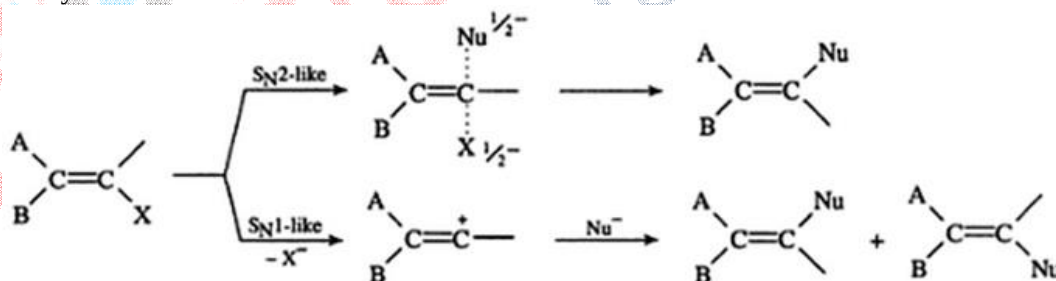


Under normal conditions, nucleophilic substitution at vinylic carbon is extremely slow compared to substitution at saturated carbon. Vinyl substrates are essentially inert towards nucleophiles. There are two reasons for this lack of reactivity. The first one is vinyl C-X bond (X- halogens). This is clearly depicted in the image above.

In fact most of contexts, vinyl halides and related compounds can be considered essentially inert towards nucleophiles. There are two reasons for this, first, a vinyl C-X bond (X = halogen, oxygen, or nitrogen) is stronger than and alkyl C-X bond because of a resonance interaction between the double bond and an unshared pair on X. This interaction also weakens and polarizes the σ -bond, which is why such compounds are reactive towards electrophilic addition.



The second reason for low reactivity of vinyl substrate towards nucleophilic substitution is that the S_N2 transition state as well as the S_N1 intermediate (a vinyl cation), are too high in energy to be readily accessible.



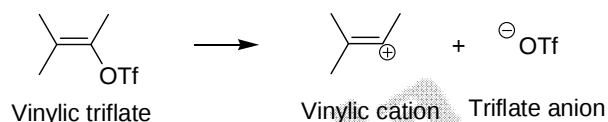
Example: The heterolytic bond dissociation energy for vinyl chloride is 207 kcal as compared with 191 kcal for EtCl and 227 kcal for MeCl. Values for the fluorides, bromides and iodides shows the similar differences. It takes 16-18 kcal more energy to break the C-X bond in a vinyl halide than in the corresponding EtCl. Except for the bond in methyl halides, this is the strongest C-X bond we have so far encountered. The bond length for vinylic C-Cl is 1.73 Å compared with 1.78 Å for the saturated C-Cl bond. A shorter bond is, in general, a stronger bond. Thus the rate determining step involves breaking of the C-X bond. The bond in vinyl halides is harder to break, and reaction is slower.

Not surprisingly, the difficulty of generating vinylic cations by heterolysis has been taken as a challenge by the organic chemist, and, in work done mostly since about 1970s, vinylic cations

have emerged as accessible intermediates with fascinating properties. Many people from many countries have been involved in this research. The vinylic cations can readily be made through solvolysis of the S_N1 kind if two conditions are met:

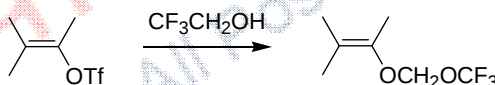
- The leaving group is extremely good one, and
- The vinylic group contains electron releasing substituents.

Most commonly used for this purpose is the super leaving group, viz. trifluoro methanesulfonate, (OTf) which is also known as triflate.



The powerful electron withdrawing F-atom (through dispersal of the negative charge) help to stabilize the triflate anion, and make the parent acid $\text{CF}_3\text{SO}_2\text{OH}$ one of the strongest Lowry-Bronsted acids known, much stronger than the familiar H_2SO_4 or HClO_4 . The triflate anion is correspondingly an extremely weak base, and one of the best leaving group in organic chemistry.

Example: Towards solvolysis, saturated alkyl triflates have been found to be 10000 to 1000000 times as reactive as the corresponding tosylates, and as much as a billion times as reactive as the chlorides or bromides. The electron releasing substituents in the vinylic moiety are very commonly aryl groups, but alkyl groups are sufficient to allow reaction by S_N1 . For example:



Substitution at vinylic carbon by other mechanism

Substitution at vinylic carbon is greatly facilitated in vinylic compounds of the type Z.CH=CH.X where Z is an electron withdrawing group e.g. CHO , R_2CO , COOEt , ArSO_2 , F. The mechanism operating in some other cases are different from the established S_N1 and S_N2 . They are described as tetrahedral mechanism and addition-elimination mechanism. We shall take up the study of this topic in future modules.

9. Summary

- S_N1 is the symbol for substitution unimolecular attended with rearrangement.
- S_N2 is the symbol for substitution bimolecular attended with rearrangement.
- These mechanisms may be appreciable to substitution in allylic system.
- The stability of the allylic radical can be utilised in the preparation of allylic halides (esp. HCl and HBr)
- Allylic bonds are often weaker and more easily broken.
- Allylic halides readily undergo substitution reactions via *either* S_N1 or S_N2 pathways.
- The carbocation formed as intermediates when allylic halides undergo S_N1 reactions have their positive charge shared by the two end carbons of the allylic system and may be attacked by nucleophiles at either site. Products may be formed with the same pattern of bonds as the starting allylic halide or with allylic rearrangement (S_N1 and S_N2).
- Allylic halides react faster than comparable alkyl halides under conditions that favour the S_N2 mechanism. The reaction is applied to organic synthesis most commonly when the allylic halide is primary.
- The label S_Ni stands for substitution, nucleophilic, internal.
- This is a third mechanism besides S_N1 and S_N2 .
- S_Ni reaction leads to retention of configuration. A typical reaction is reaction between optically active $\text{C}_2\text{-phenyl ethanol}$ with thionyl chloride. The product $\text{C}_2\text{-phenyl ethyl chloride}$ has the same configuration as the starting alcohol.
- Vinylic substrates ($\text{CH}_2=\text{CH-X}$) are essentially inert towards nucleophilic substitution.