The Williamson Ether synthesis is the easiest, and perhaps the fastest, way to create ethers.

Introduction

Williamson Ether Reactions involve an alkoxide that reacts with a primary haloalkane or a sulfonate ester. Alkoxides consist of the conjugate base of an alcohol and are comprised of an R group bonded to an oxygen atom. They are often written as RO\(^-\), where R is the organic substituent.

S\(_{n2}\) reactions are characterized by the inversion of stereochemistry at the site of the leaving group. Williamson Ether synthesis is not an exception to this rule and the reaction is set in motion by the backside attack of the nucleophile. This requires that the nucleophile and the electrophile are in anti-configuration.

Ethers are prepared by S\(_{n2}\) reactions

Ethers can be synthesized in standard S\(_{n2}\) conditions by coupling an alkoxide with a haloalkane/sulfonate ester. The alcohol that supplies the electron rich alkoxide can be used as the solvent, as well as dimethyl sulfoxide (DMSO) or hexamethylphosphoric triamide (HMPA).

For example
Intramolecular Williamson Ethers

You can also use the Williamson synthesis to produce cyclic ethers. You need a molecule that has a hydroxyl group on one carbon and a halogen atom attached to another carbon. This molecule will then undergo an $S_N_2$ reaction with itself, creating a cyclic ether and a halogen anion. Another way of deriving ethers is by converting halo alcohols into cyclic ethers. This reaction is prompted by the deprotonation of the hydrogen attached to the oxygen by an $OH^-$ anion. This leads to the departure of the halogen, forming a cyclic ether and halogen radical.

Another factor in determining whether a cyclic ether will be formed is ring size. Three-membered rings along with five membered rings form the fastest, followed by six, four, seven, and lastly eight membered rings. The relative speeds of ring formation are influenced by both enthalpic and entropic contributions.

Enthalpy and Entropy Contributions

Ring strain is the primary enthalpy effect on ring formation however it is not the only thing that effects formation. If this were the case, rings with the most strain would be formed the slowest. The reason why this is not the trend for ring formation is because of entropy conditions. Smaller rings have less entropy making them more favorable because of less ordering of the molecule.

However, the reason why ring formation does not follow this trend is because of another factor called the proximity effect. The proximity effect states that the nucleophilic part of the carbon chain is so close to the electrophilic carbon that a small amount of ring strain is evident in the ground state of the molecule. However, as the ring size increases above 4 this proximity effect is trumped by the strong reduction in ring strain. Five and six membered rings have less strain allowing them to form faster. However, as rings get larger (8,9,10 etc. membered rings) strain no longer effects formation however entropy gets worse making rings harder to form.

References

Problems

1) $\text{HO}($CH$_2$)$_3$CH$_2$Cl $+ \text{HO} \xrightarrow{\text{HMPTA}}$ 

2) $\text{Br}$ $\xrightarrow{\text{DMSO}}$

3) Synthesize the following product starting with an alcohol

4) $\text{CH}_3\text{CH}_2\xrightarrow{\text{DMSO}} + \text{CH}_3\text{CH}_2\text{Br}$

5) Synthesize the following product using a haloalkane as a starting reactant

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