9.6: Synthesis of Target Molecules- Introduction of Retrosynthetic Analysis

We have learned three major types of reactions so far, nucleophilic substitution, elimination and halogenation of alkane (radical substitution), now we will see how to put the knowledge of these reactions together for application, that is to design synthesis route for a target (desired) compound from available starting materials.

Building larger, complex organic molecules from smaller, simple molecules is the goal of organic synthesis. Organic synthesis have great importance for many reasons, from testing the newly developed reaction mechanism or method, to replicate the molecules of living nature, and to produce new molecules that have potential applications in energy, material or medicinal fields.

It usually take multiple steps, from several to 20 or more, to synthesize a desired compounds, and therefore it would be challenging to visualize from the start all the steps necessary. The common strategy to design a synthesis is to work **backward,** that is instead of looking at the starting material and deciding how to do the first step, we look at the product and decide how to do the last step. This process is called **retrosynthetic analysis,** the technique applied frequently in organic synthesis. We will introduce the basic ideas of retrosynthetic analysis here, and for practice purpose the starting material is always defined for our examples.

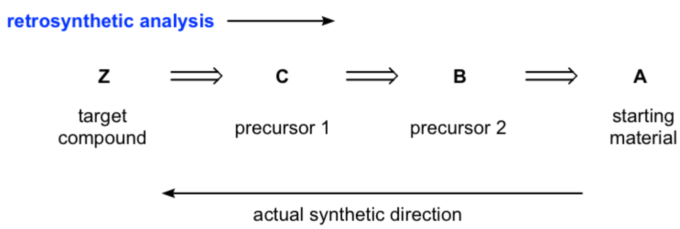
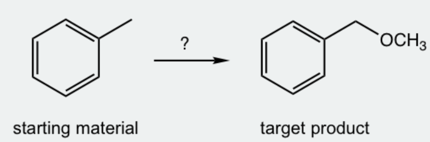


Figure 9.6a Retrosynthetic analysis

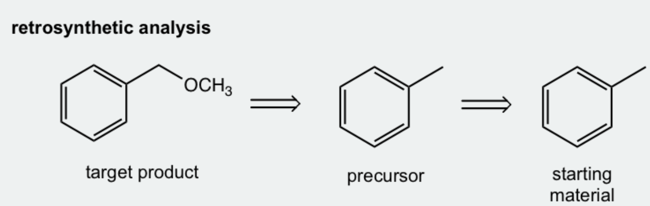
Retrosynthetic analysis can usually be shown in the above way, with the open arrows indicate that the analysis is **backward**. We first identify the precursor 1 that could react in one step to make the target compound, then identify the next precursor that could react to give precursor 1, and repeat the process until we reach the starting material. Please note that the analysis is the way to show the "thinking or ideas" for solving the problem, so typically the reagents/conditions required for each step are not specified until the synthesis route is written in the forward direction. Also it is very possible you may come up with multiple routes, with different precursors, then the most efficient synthesis route can be determined by evaluating the possible benefits and disadvantages of each path.

Examples

Design the synthesis route of methoxybenzene starting from toluene.

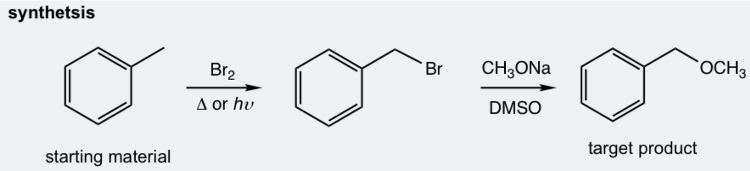


Approach: The target compound is an ether. We have learned that S_N2 reaction is a reasonable way to introduce different functional groups by applying different nucleophiles (**section 7.3**), that said the reaction between CH_3O^- (nucleophile) and halide gives the desired ether, and the halide can be the "precursor 1". The halide precursor can then be directly connected with the starting material, toluene, through the halogenation that we just learned in this chapter. This is an easy example that only involve two steps.



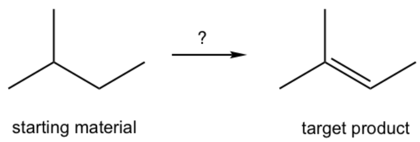
Solutions:

The analysis can then be transferred to the solution of the question by showing the reactions in forward direction and include the reagents/condition for each step.



Synthesis route design is a rather challenge topic that need lots practices. In order to do that well, you should be very familiar with all types of reactions in terms of how the functional groups transformed, and what reagents and conditions involved. Sometimes some reaction features, like stereochemistry will be useful as well.

Exercises 9.4 Design the synthesis route.



Answers to Practice Questions Chapter 9