Chapter 7

Organic Synthesis and Retrosynthetic Analysis Problems

Retrosynthetic analysis is a technique for solving problems in the planning of organic syntheses. This is achieved by transforming a target molecule into simpler precursor structures without assumptions regarding starting materials.

Each precursor material is examined using the same method. This procedure is repeated until simple or commercially available structures are reached. E.J. Corey formalized this concept in his book *The Logic of Chemical Synthesis*.

The power of retrosynthetic analysis becomes evident in the design of a synthesis. The goal of retrosynthetic analysis is structural simplification.

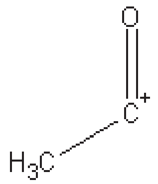
Often, a synthesis will have more than one possible synthetic route. Retrosynthesis is well suited for discovering different synthetic routes and comparing them in a logical and straightforward fashion. A database may be consulted at each stage of the analysis, to determine whether a component already exists in the literature. In that case, no further exploration of that compound would be required.

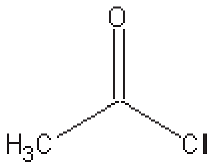
Disconnection: A retrosynthetic step involving the breaking of a bond to form two (or more) synthons.

Retron: A minimal molecular substructure that enables certain transformations.

Retrosynthetic Tree: A directed acyclic graph of several (or all) possible retrosyntheses of a single target.

Synthon: An idealized molecular fragment. A synthon and the corresponding commercially available synthetic equivalent are shown below:

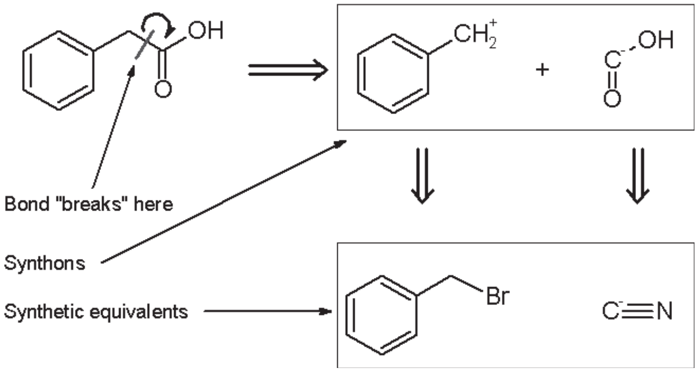




Target: The desired final compound.

Transform: The exact reverse of a synthetic reaction; the formation of starting materials from a single product.

Example: An example will allow the concept of retrosynthetic analysis to be easily understood.

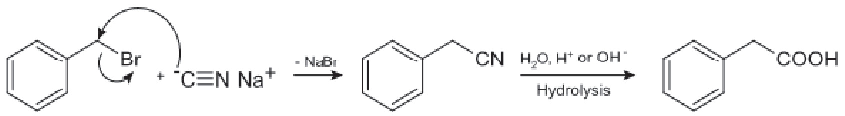


In planning the synthesis of phenylacetic acid, two synthons are identified. A nucleophilic "-COOH" group, and an electrophilic "$PhCH_2^+$" group. Of course, both synthons do not exist per se; synthetic equivalents corresponding to the synthons are reacted to produce the desired product. In this case, the cyanide anion is the synthetic equivalent for the ^-COOH synthon, while benzyl bromide is the synthetic equivalent for the benzyl synthon.

The synthesis of phenylacetic acid determined by retrosynthetic analysis is thus:

$$PhCH_2Br + NaCN \rightarrow PhCH_2CN + NaBr$$

$$PhCH_2CN + 2\ H_2O \rightarrow PhCH_2COOH + NH_3$$



In fact, phenylacetic acid has been synthesized from benzyl cyanide, itself prepared by the analogous reaction of benzyl chloride with sodium cyanide.