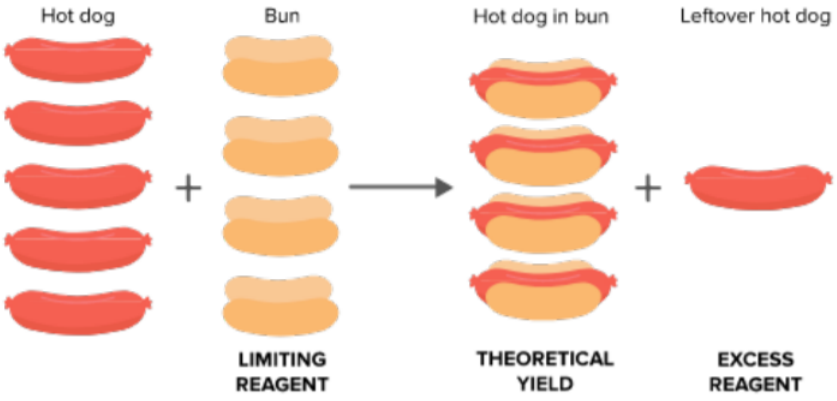
6.3: Reaction Design Concepts

Reaction Design and Efficiency

Green chemistry is all about increasing the overall efficiency of a reaction in terms of numerous criteria. In general, we try to mimic biological reactions because they are among the most efficient, low energy, and atom conserving reactions at our disposal. In terms of the "perfect" chemical reaction, we are talking about:

- *Selectivity:* we want to make one thing and one thing only to ensure that we don't have contamination or other issues to content with the require cleanup, purification, or multi- step pathways.
- *Efficiency*: This term refers to the overall energy, time, and material inputs relative to the final product required. How intense is the process needed to obtain a final product? Obviously, a more efficient process/reaction will require much less inputs. In an ideal scenario, a product occurs spontaneously without very little input.
- *Safety*: Although we don't talk about it much, the criterion of safety for a reaction or process must be paramount and very redundant given "Murphy's Law". Green chemistry is truly a discipline that is framed in the overall theme of safe performance and operation for a process or else it insists upon a no-go juncture point.
- *Solventless*: Again, the overall inputs are minimized in any reaction, and this is just one of the many criteria to ensuring efficiency and lowest impact. To do a reaction solventless means allowing self-reaction to occur with or a bimolecular reaction with other reagents in the absence of a solvent. Although many biological reactions occur in a solvent, ideally, it would be best to avoid if possible because of the many issues surrounding solvents: disposal, clean up, concentration-based reactions (depend on kinetics), and in the case of water, its precious nature for food, drinking, washing, etc.
- *Low or no energetics*: Here we try to approach an ideality for energy conservation in which we reduce the need for high heat, high pressure, long times, etc. Ideally, we would use the energy available to us without attempting to burn gas, coal, employ electricity (power grids), etc.
- *Chemical yield*: In most standard chemistry reaction descriptions, we tend to emphasize the "yield" of a reaction as the chief parameter for assessing the reaction efficiency or utility. A low yield reaction would be undesirable because of the lack of return on the process. Chemical yield is defined as the moles of desired products obtained as a ratio to the possible moles (theoretical) possible expressed as a percentage.

Let's give an excellent intuitive example from the Khan Academy (www.khanacademy.org/science/...-percent-yield): Let's assume you have five hot dogs and four hot dog buns. Obviously, you will have one hot dog in excess.



In terms of chemical reactions, the hot dog buns are the limiting reagent and the leftover single hot dog is the excess reagent; thus, four complete hot dogs are the theoretical yield, assuming the hot dogs and buns combine in a one-to-one ratio (you've got to balance the reaction first). In any chemical reaction, the limiting reagent is the reactant that determines how much of the products can be made. The other reactant(s) is/are in *excess*.

How do we measure yield more efficiently?

Typically, chemical yield focuses on a part of the reaction, i.e., our desired product based on the complete reaction of the limiting reagent. However, in many cases, the overall efficiency from a green chemical perspective is compromised despite high chemical yields. Consider the "Gabriel Synthesis":

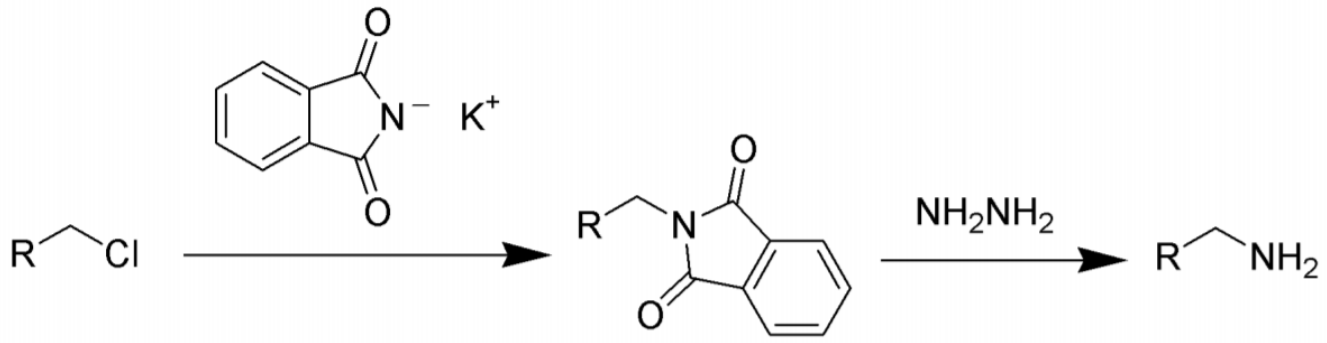


Figure 6.3.13: A representation of part of the classical Gabriel Synthesis whose product is a primary amine. http://www.wikiwand.com/en/Gabriel_synthesis

The reaction transforms primary alkyl halides into primary amines. In Figure 6.3.13, only the latter half of the reaction/synthesis is shown! Traditionally, the reaction uses potassium phthalimide (an $–NH_2$ synthon) to homologate the alkyl which is later coupled to the amine. In the Gabriel Synthesis, the phthalimide anion is employed as a surrogate of H_2N^-. The entirety of the reaction is shown in Figure 6.3.14:

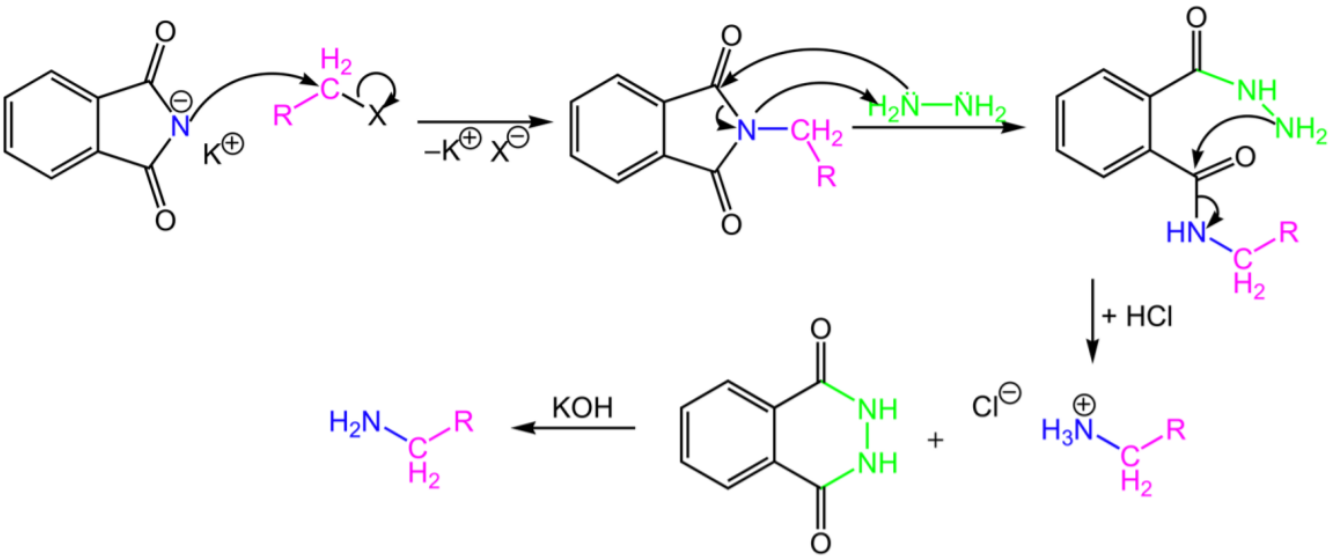


Figure 6.3.14: The Gabriel Synthesis that starts with the amine synthon (the first reactant at the left) that after four steps yields the desired primary amine. commons.wikimedia.org/wiki/File:Gabriel_synthesis_mechanism.png

In chemical yield methodologies, we do NOT account for the stream of by-products that amass during a reaction or set of reactions. In the above case, we have the following waste products: potassium halide (K-X), potassium chloride (KCl), and phthalhydrazide (see Figure 6.3.13 for the structure – the aromatic compound, second from right). Unbelievably, this array (especially the hydrazide) make up a huge fraction of wasted atoms that do not contribute in any way to the efficiency of the reaction. Because of the incredible "atomic" waste, we have a reaction with a very poor "atom economy".

Atom Economy

This is a concept that was first formalized by Trost. 1 Atom economy (atom efficiency) is the conversion efficiency of a chemical process in terms of all atoms and the desired product(s). It is one of the most singularly powerful definitions for understanding the "greenness" of a reaction and its potential usefulness.

Atom economy can be written as:

$$Atom\ Economy\ (\%) = \frac{Molecular\ Mass(MW)\ of\ Desired\ Product}{Molecular\ Mass(MW)\ of\ All\ Reactants} \times 100$$

As we already alluded, in an ideal chemical process, the amount of starting materials equals the amount of all products generated and no atom is wasted. If this is not the case, this is a genuine concern for raw materials that have a high cost or due to economic and environmental costs of disposal of the waste.

In addition to high-yielding process such as the Gabriel Synthesis that result in substantial byproducts, we also have the Cannizzaro Reaction[2] where 50% of the reactant aldehyde becomes the other oxidation state of the target and the Wittig[3], where high-mass phosphorus reagents are used but become waste.

A Diels-Alder reaction is an example of a very atom efficient reaction that also can be chemo-, regio-, diastereo- and enantioselective. Catalytic hydrogenation comes closest to being an ideal reaction that is extensively practiced both industrially and academically.[4]Poor atom economy is common in drug (pharmaceutical) synthesis, and in research. For example, during the synthesis of an alcohol by reduction of an ester with lithium aluminum hydride, the reaction produces a huge amount of aluminum salts. The cost can be considerable.

Experimental atom economy

In this derivative calculation of atom economy, we account for the actual quantities of reagents used in a ratio of theoretical yield of product total mass of reactants used as a percentage. Or equivalently, we can calculate the mass of reactants utilized in the desired product divided by the total mass of all reactants as a percentage

Percentage yield x experimental atom economy

This is considered the ultimate measure of the efficiency of a reaction. In this case, you multiply the chemical yield of the product by the experimental atom economy to obtain a true measure of the atom efficiency of the reaction

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