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Applying green processes and techniques to simplify reaction work-ups

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1. Introduction

When planning a reaction, not only its set up but also the way in which the product will be isolated and purified must be carefully taken into consideration. The work-up of a reaction is a very important process once products of high purity are desirable and some modern separation techniques have been developed to increase its efficiency.[1] It generally involves quenching a reaction and isolating the product from the reaction mixture, followed by a purification step. In some cases, the procedure is so tedious and laborious that takes longer than the reaction itself. The work-up procedures for many reactions apply the time-consuming sequence of: extraction of the product from the aqueous phase with an organic solvent (liquid-liquid extraction), washing the combined organic phases with some aqueous solution, drying of the organic

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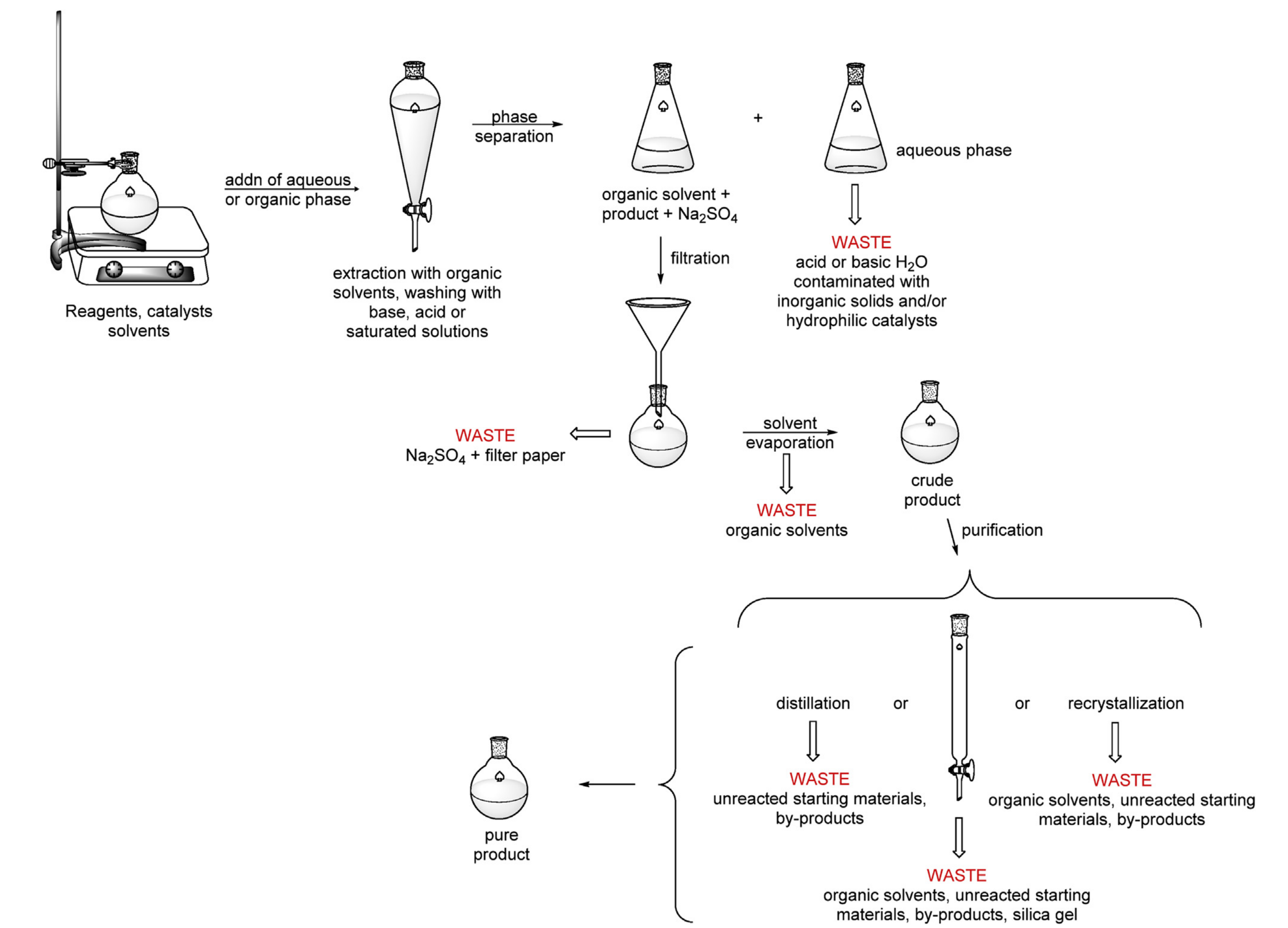
phase with a suitable drying agent, filtration and evaporation of the solvent (Scheme 1). After all these steps, the crude product usually has to be purified by distillation, recrystallization, chromatography, etc. In each of these steps, waste is continuously generated.

generates toxic or non-toxic wastes (first principle) can potentially turn the work-up process more difficult and if a reaction has a big atom economy (second principle), potentially less waste will be generated. Much care should be taken when working-up



Scheme 1. The usual organic reactions work-up scenario.

Although simple, some aspects of this strategy deserve comment. First of all, the extraction step usually uses a toxic and/or volatile organic solvent (e.g., CH_2Cl_2, $CHCl_3$, EtOAc, Et_2O), which poses several environmental and health problems. Secondly, the formation of emulsions is common during this stage, contributing to decrease the efficiency of the process. Furthermore, the amount of waste generated can be appreciable and depends upon each specific reaction and its scale. Last, but not least, the purification step tends to be troublesome and in most cases requires the use of more organic solvents.

The advent of Green Chemistry in the 1990's has been gradually changing the way chemistry is thought and also taught.[2] Since then, several efforts have been taken to spread the ideas of sustainable and environmentally benign ways to do chemistry[3] and one of the main issues is how to apply these ideas to simplify reaction work-ups. It is very much clear that the 12 principles addressed by Green Chemistry were designed aiming a higher synthetic efficiency in better chemical processes with less environmental impact (Fig. 1).[2a] Most of these principles are strictly related to the work-up process. Usually, everything that a reaction in which hazardous chemicals are employed or if the products are toxic (third and fourth principles), increasing the time and complexity of the process. The use of safer solvents or no solvent at all in a reaction (fifth principle) carried out at room temperature and pressure (sixth principle), under catalysis (ninth principle) and without the need for reagent derivatization (eighth principle) greatly simplifies the work-up and leads to a greener and safer approach (12^{th} principle). Ultimately, these principles are able to deliver both economic and environmental benefits[4] and the important thing to consider is that they are driving the need not only to perform reactions in a green and safer manner, but also to work-up these reactions in a similar fashion.

Perhaps the major contribution from the concepts of Green Chemistry is the search for alternative reaction media.[5] These reaction media are usually associated with a method or strategy which enables performing a reaction under a greener fashion.[6] Fig. 2 summarizes this approach. For instance, a reaction can be carried out in an ionic liquid under microwave irradiation or be a solvent-free reaction using grindstone chemistry.