How to Succeed in Multi-Step Organic Synthesis

There are several key components to achieving success in multi-step organic syntheses, including: knowledge of a large number of synthetic transformations, technical skills, and diligence. You can achieve considerable success with hard work and superior technical skills, but the real advantage comes from mastering the intellectual and tactical aspects of how to efficiently accomplish multi-step synthesis. The best way to increase your repertoire of transformations is to read the literature and attend seminars and group meetings. The development of technical skills requires practice, which means time spent in the lab. While a thorough reading of the literature can often save you weeks of laboratory effort, there is no substitute for spending the time in the laboratory doing experiments. It is the time that you can spend doing laboratory research that is the most precious and limited resource. You must learn to use it efficiently. Work smarter. To get the most out of your time, the following points should be strictly followed.

1) Define your goals. You should always know what you are trying to accomplish and why. Set realistic and well-defined targets and *do not get side-tracked or stop until you get there*.

2) Develop and follow a workable plan to accomplish your goals.

Establish well-defined strategies to accomplish your goals. Once you embark on a synthetic sequence, *do not get side-tracked or stop until you either finish it, or some insurmountable obstacle arises*. Much time is wasted by prematurely abandoning a specific approach for another due to a couple of initial mis-steps. Sometimes one needs to simply put their head down and drive forward. Quitting is habit forming. Periodically , however, one does need to step back and re-evaluate their plan and its effectiveness relative to viable alternatives. But, if a plan is worth pursuing in the first place, then it is worth pursuing diligently.

Efficiency is generally inversely proportional to the number of individual chemical transformations involved. Convergent approaches are often better than linear ones. However, there are notable exceptions where a linking together a number of high yielding linear steps can give consistently superior results over a shorter sequence that involves inconsistent or low yielding transformations. Do not be intimidated by length alone, but always look for short-cuts.

3) Budget your material.

A primary objective of multi-step synthesis is always to convert starting materials and earlier intermediates into advanced intermediates and final products. It is a fact that you will always finish with less than you start with. To end up with an appreciable amount of material in a reasonable amount of time, it is absolutely necessary that you budget your material wisely. The further into a synthetic sequence you go, the more valuable the material becomes because there will be less of it at each step and that which does remain represents your cumulative time and effort. Two guiding principles here are to **never commit all of your material to one reaction**, and **minimize the number of times you have to unexpectedly go back to the beginning of a synthetic sequence**. These, of course, are interrelated; the more often you commit the bulk of your material to a single transformation, the more often you will have to go back to the beginning because that attempted single transformation will eventually fail. You should anticipate performing each step in a multi-step synthesis several times, each time with only a portion of your material. When you come up short from a failed transformation on a small portion of your material, it's a loss of the time that it took you to perform that experiment and the relatively small amount of material. However, when you *foolishly* attempt a transformation on the bulk of your material and something goes wrong, it can mean having to go all the way back to the beginning and a cost of weeks or even months of your time. It is well worth the extra day or two it may take to process your advanced synthetic intermediates by cautiously performing even standard transformations on only a portion of the material at a time.

It depends upon the nature of the transformation and the amount of material you have in hand, but as a rule of thumb one would usually first perform a new reaction on advanced synthetic intermediates on a 1-10 mg scale. If that works well, then one may perform a step-wise scale up to 100 mg then to 1 g or **not more than one-third of the remaining material at a time**.

A corollary to the above is that you should ensure that you have substantial quantities of key advanced synthetic intermediates by going back to earlier stages in the synthetic sequence and bringing up material whenever you have the opportunity (i.e. in your free time). **Do not wait until you run out of your most advanced synthetic intermediates before doing this**. Cycling back during intermediate stages of a synthesis can keep you quite busy, but it will allow you to complete the overall multi-step synthesis in a much shorter overall period, and that is one of the chief goals.

4) Budget your time.

Learn to perform several operations at the same time. This is the single-most distinguishing factor that separates successful synthetic chemists from the rest. Accomplished chemists can make a surprising amount of progress in a single day. Doing one reaction at a time is fine for beginning undergraduates, but will not get you very far in multi-step synthesis or as a synthetic chemist. This is true for accomplishing routine synthetic sequences, as well as for more challenging problems. It is wholly unsatisfactory to perform but one task at a time, let alone one reaction per day. When faced with more difficult synthetic challenges, you should develop a multidimensional, rather than a linear, approach towards progressing along a synthetic sequence. This means that you should consider a number of likely alternatives and rapidly survey them **simultaneously** (that means at the same time in a parallel fashion, not sequentially one after another) on small scale. **Set up more than one reaction at a time.** Always look for short-cuts. For example, try to consider and identify alternative synthetic pathways to get you from intermediate A to product D without going through intermediates B and C. There will usually be more than one unique pathway from A to D. Another important, yet more subtle, aspect of time management is to identify the minimal amount of time that should be devoted to successfully accomplish an individual transformation. In many instances it will save you time overall if you expend a little extra effort to carefully purify your reagents and intermediates, and carefully set up and execute an experiment. Other transformations that are far more tolerant of impurities may be accomplished without devoting extra time to lengthy purifications or separation of isomers. Design your experiments and synthetic sequences to minimize the necessity for lengthy and difficult separations. **Minimize the amount of time spent doing preparative scale chromatography**.

Finally, **plan ahead** and "Don't put off until tomorrow what you can accomplish today." Each day, you should ask yourself "what can I do today so that my project will be significantly advanced by tomorrow." It is especially useful to ask this before stopping at the end of the current day. The answer may be setting up another transformation to go overnight; assembling glassware and chemicals for the next step; reserving NMR time; washing glassware; purifying products, reagents, products, or solvents; characterizing that product today; searching the literature to find alternatives; et cetera. There is always *something* that you can do to place your project at a strategic advantage for the next day. You should not sleep well unless your research is advancing.