Speed to Success – Resins, Microwaves and New Paradigms in Synthesis Chemistry

Chemical synthesis has been around for a long time - Hermann Kolbe first used the term 'synthesis' in the way in which modern chemists understand it in the 19th century[1]. Many of the important named reactions that are still used in laboratories today of a similar pedigree, for example the Wurtz reaction which involves two alkyl halides reacting together with sodium to form a new alkane, was first published in 1855[2]. But as always in scientific practice, trends exist that define current thinking in chemistry. In this article we will discuss a recent trend in organic chemistry, the 'speed to success', and how microwave synthesis and solid-bound resin reagents help to achieve this goal, especially in those laboratories such as in medicinal or agricultural chemistry where synthesizing a target molecule quickly is the criterion of success.

From Combinatorial Chemistry to the Speed to Success

Ten to fifteen years ago organic chemistry was in the midst of a revolution. Combinatorial chemistry was at the cutting edge, and procedures, instruments and mind-sets were changing to embrace this new approach. Traditionally, new molecules had been designed by understanding the fundamentals of the structure-property relationship, and carefully constructing molecules which enhanced the desired outcome. This targeted synthesis could yield great results, but it was time-consuming, required a keen understanding of the problem being solved, and was ultimately costly. In contrast, a combinatorial chemistry approach required much less understanding and took a 'scattergun' approach – large 'libraries' of target molecules could be synthesized simultaneously, and screened against a key test. Candidate molecules that showed promising behavior could be isolated and would form the basis of further screening. The idea was that molecules would be uncovered that had never been considered for a particular property as aspects of their structure-property relationship were unknown, and that at the same time large libraries of molecules would be made available to screen against other criteria in future assays.

Ultimately, combinatorial chemistry did not lead to a revolution in the output of chemical laboratories. For example in medicinal chemistry, very few regulated drugs have been synthesized as a direct result of combinatorial chemistry. Limitations in key chemical spaces such as chirality and chemical rigidity are thought to be some of the reasons why combinatorial chemistry approach has not led to an increase in synthetically derived drugs.[3] Instead chemists have increasingly returned to more traditional structure-property based investigations, and the speed to success has become key.

Speed to success in organic synthesis can be defined as the rate at which a paper-concept of a new target molecule can be converted into the actual product. In other words, the speed of the synthetic process. Many chemists in industrial laboratories are judged on the number of target molecules they can synthesize in a given time frame. Obviously for these scientists, any method by which the synthetic procedure can be enhanced is beneficial. We will discuss below two methods that can be used to increase the speed of chemical synthesis – the use of resin-based reagents, and microwave synthesis.

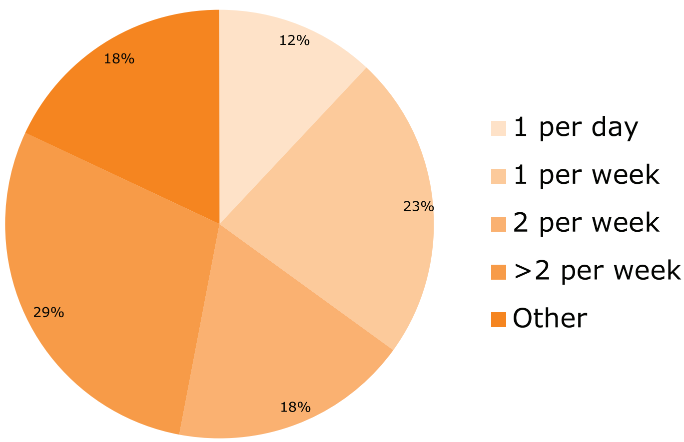


Figure 1. Market survey of synthetic chemists – how many target molecules do you need to synthesize?

Resin-bound Reagents and Scavengers

Many traditional chemical reagents used in common synthetic routes share a common trait – they leave trace remnants after reaction are extremely difficult to remove. In some cases, including those where metals such as palladium are employed, removal of all traces is vital if the compound is to be used in biological applications. Traditional approaches to removing unwanted impurities include washing steps, precipitations/ recrystallizations or chromatography, but all these techniques are slow and in some cases expensive. This is where resin-bound reagents can be a real benefit. In this approach, one of the chemicals used in the synthetic transformation, or a chemical specifically designed to remove unwanted starting materials, is bound onto the surface of a solid support, typically silica or a cross-linked polymer. This supported reagent can be added to the reaction as normal but the real benefit comes when the reagent needs to be removed. As the reagent is physically bound to the solid support, a quick and simple filtration is all that is required to remove it, a common process in any laboratory and on any scale.

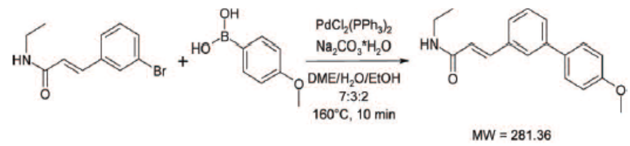
Many supported reagents consist of one particular chemical that may be used in a small range of chemical processes, such as a support triphenyl phosphine and Wittig chemistry. By their very nature, these reagents are utilized in specific applications. However, one class of supported reagents that can find much more widespread use are the scavenger resins, supported reagents designed to remove specific classes of compounds from a reaction, for example TMT (trimercaptotriazine) for the removal of palladium and other metals. Traditional methods of removing palladium are expensive and time-consuming, for example repeated washing or the reaction in a variety of expensive solvents may be necessary to remove all of the metal. However using a supported scavenger like MP-TMT, it is possible to bind metal ions to the support and then simply remove by filtration. Scavenger resins for metals, solution-phase reagents and reaction side-products are an important component of modern chemical synthesis procedures, and greatly increase the speed to success of a synthetic chemistry laboratory.

Biotage supply a wide range of supported chemicals from scavengers to reagents, for more information visit:

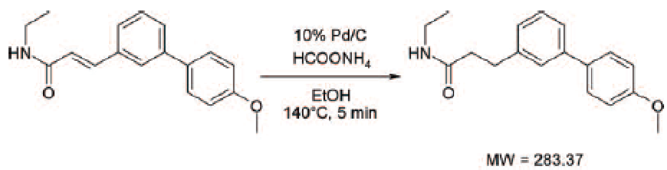
http://biotage.com/product-group/reagents-and-scavengers

Microwave Synthesis

The Arrhenius equation tells us that for a chemical reaction a ten degree rise in temperature doubles the reaction rate, so it is no surprise that traditional chemical synthesis often involves heating samples to high temperatures. Unfortunately, even with conventional heating, reactions can be very long with reflux times of many hours. Obviously this is a barrier to the rapid synthesis of target molecules for further investigation. In contrast to conventional heating, microwave irradiation is becoming a well-established method of increasing the reaction rate of chemical processes as elevated temperatures can be achieved quickly and under a high level of control. Using microwave assisted organic synthesis (MAOS), a reaction that might originally have taken hours can be achieved in a few minutes, with increased reaction efficiency and therefore compound purity at the same time. Most microwave systems are batch designs, allowing sequential reactions to be performed under identical, carefully controlled conditions, ideal for combinatorial chemistry approaches. However, these systems are also ideal for the rapid synthesis of a target molecule, as complex multi-stage synthetic procedures can be performed rapidly, and resin-based reagents can also be used in this approach, allowing benefits from both technologies to be employed in a synthetic plan. As a result increasing numbers of pharmaceutical and industrial laboratories make use of microwave assisted organic synthesis (MAOS) to trial new reactions and rapidly develop new molecules on the small scales required for preliminary screening, and microwave heating has become an important strategy in increasing the speed to success of a synthetic process.



Step 1. Suzuki reaction.



Step 2. catalytic hydrogenation.

Biotage is a pioneer of microwave synthesis, and has a large database of chemical reactions that can be used a building blocks in synthetic routes to new molecules. For details of Biotage microwave systems, please visit:

http://biotage.com/product-area/organic-synthesis

Summary

Trends on chemical synthesis have changed over recent years, with a more targeted approach to molecular design becoming more prevalent. As a result, the speed with which a new compound can be synthesized is key to an efficient laboratory. Biotage manufacture consumables and instruments that work within this approach to help chemists maximize their output. Resin-bound scavengers and reagents help to speed the steps of a chemical synthesis and produce a pure compound, and microwave assisted heating can be used to reach high reaction temperatures quickly and under high levels of control.

References

1. Rocke, Alan J. (1993). The Quiet Revolution: Hermann Kolbe and the Science of Organic Chemistry. University of California Press. ISBN 0-520-08110-2.
2. Adolphe Wurtz (1855), "Sur une nouvelle classe de radicaux organiques", Annales de chimie et de physique 44: 275–312.
3. M. Feher and J. M. Schmidt "Property Distributions: Differences between Drugs, Natural Products, and Molecules from Combinatorial Chemistry" J. Chem. Inf. Comput. Sci., 43 (2003) 218