New Experimental Techniques for Organic Synthesis

A Review of Modern Technologies

Chemical Synthesis Beyond the Round Bottom Flask

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Today's researchers working in synthetic organic chemistry are under increasing pressure to discover and develop new and improved chemical reactions and processes as quickly as possible. To be successful, chemists use various techniques to build comprehensive knowledge of the reaction as they study it, understand it, and adapt it for use in a wide range of industrial applications.

While analytical technologies that support the synthesis laboratory have changed dramatically, chemical synthesis itself has remained largely unchanged for over fifty years. During that time the round bottom flask has been the workhorse for the synthesis lab. But it has its drawbacks. Heating and cooling of the reaction mass can be awkward and imprecise, and maintaining a temperature set point over several hours is difficult. In many cases, synthesis steps are impossible to perform unless someone is present to supervise the reaction and repeating a synthesis is not always straight forward.

Chemists are always looking for novel ways to meet the challenges they face. METTLER TOLEDO has been working with chemists to develop a new line of tools to help scientists develop a greater understanding of the reactions they study, and redefine the way organic syntheses are researched and performed while maintaining their current workflow. This white paper discusses how newly developed techniques for chemical syntheses are eliminating key challenges, and introduces the concept of chemical synthesis without the traditional round bottom flask.

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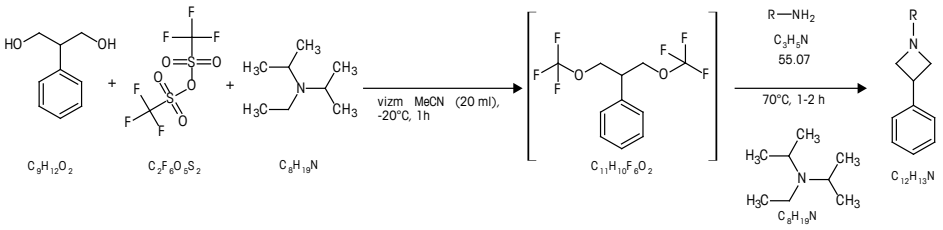
Temperature is Critical, and Should be Easy to Control

Traditionally in organic chemistry, four temperatures have been consistently used: -78°C, 0°C, room temperature and reflux. Many chemical reactions have been developed at these temperatures because they are easy to maintain. But the reality is that many more temperatures exist, and are frequently used, as reactions occur in a more desirable manner when they are run at temperatures in between these four classic values. Specificity, impurities and yield are all important factors that the organic chemist must design into the reaction, and these can all be dependent upon the temperature at which the reaction is run.



In this example, the decision was taken to run the chemistry in an EasyMax™ synthesis workstation. The chemistry will be run at a temperature of -20°C in order to prevent unwanted reactions. Also, the reaction generates a strong exotherm which needs to be controlled, and the temperature selection helps in this task. Note the temperature trace (Figure 1.), which shows the progression of reaction temperature through the experiment. The reaction is cooled to -20°C simply by entering the desired temperature on the touch pad of the synthesis workstation. The reaction mass quickly goes to -20°C. The temperature is then held throughout the first part of the experiment (around two hours).

Note there are a couple of minor increases in temperature. This is caused by the action of dosing reagents, which were at room temperature when dosed. The temperature change caused by the addition of these reagents is controlled and the temperature is returned to -20°C with no intervention from the chemist. Also note the duration of the entire reaction – around four hours. In this example the chemist was not required to take any action in order to maintain the temperature at the desired level (-20°C), even though there were significant exotherms produced due to the highly reactive nature of the reagents. The reaction is controlled by the synthesis workstation, and side reactions and decompositions are avoided.

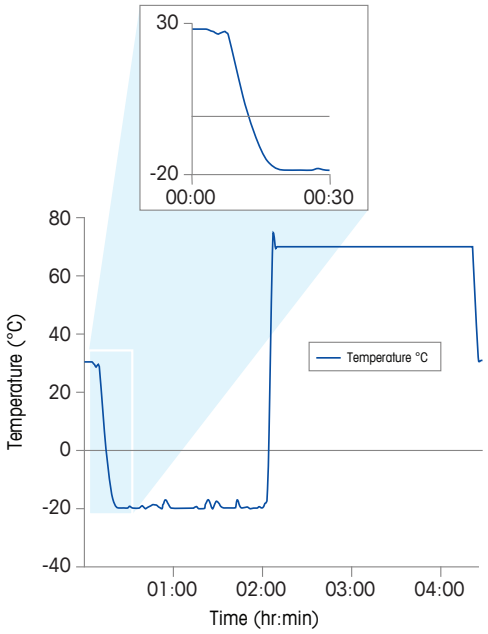


Figure 1. Temperature profile of the reaction showing attainment of -20°C

"EasyMax™ is the first controlled reactor system in an organic chemistry lab that is completely accepted by chemists and already supersedes traditional round bottom flasks."

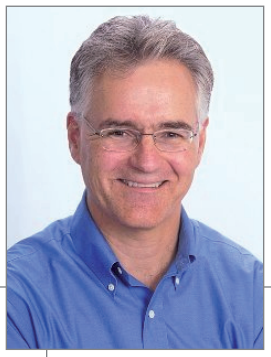
Luc Moens
Research Fellow, Chemical Process & Research Development, Johnson & Johnson, Belgium

Reactions Need Supervision, but You Don't Have Time

Running a reaction can require a great deal of supervision. Temperature set points must be closely controlled, ice added to ice baths, and reagents must be added. But this is time consuming and ideally a reaction should be supervised by someone, or even something, else. Imagine a situation where the chemist doesn't have to worry if the temperature is correct, reagents are added, exotherms are controlled, and no reaction event is missed.

Looking at the example, a multi-step addition of the reactant was required over a long period of time. While this is not always a difficult task on its own, it requires constant attention and supervision. Using traditional methods, a chemist would have performed this reaction by spending two hours supervising the temperature of the reaction (adding ice to maintain the temperature), and also needed to constantly monitor the addition of the reactants by adjusting the dropping funnel. However, it is now possible to set the temperature (as discussed above), and also to set the reagent addition. The synthesis workstation keeps the temperature stable, and the reagents are added according to the recipe (Figure 2.). Now the chemist can walk away and concentrate on something else, like designing a new reaction sequence. Requiring less supervision provides an additional benefit. Many reactions require some kind of hold time. In this example, the reaction is heated after dosing is complete, and then held for a period of two hours. Previously, this may have required supervision at the end of the day. The reaction may not have even been completed if some action was required overnight. Now, the reaction can be left to complete on its own, and the synthesis workstation can supervise and even control events such as temperature changes and additions. The chemist can move on to other things.

"Currently, our chemists and engineers are utilizing EasyMax™ on a daily basis for both early and late-stage process development in a variety of applications and venues."



Dr. Marty Guinn
Chemical Development, Pfizer
Pharma Therapeutics, USA

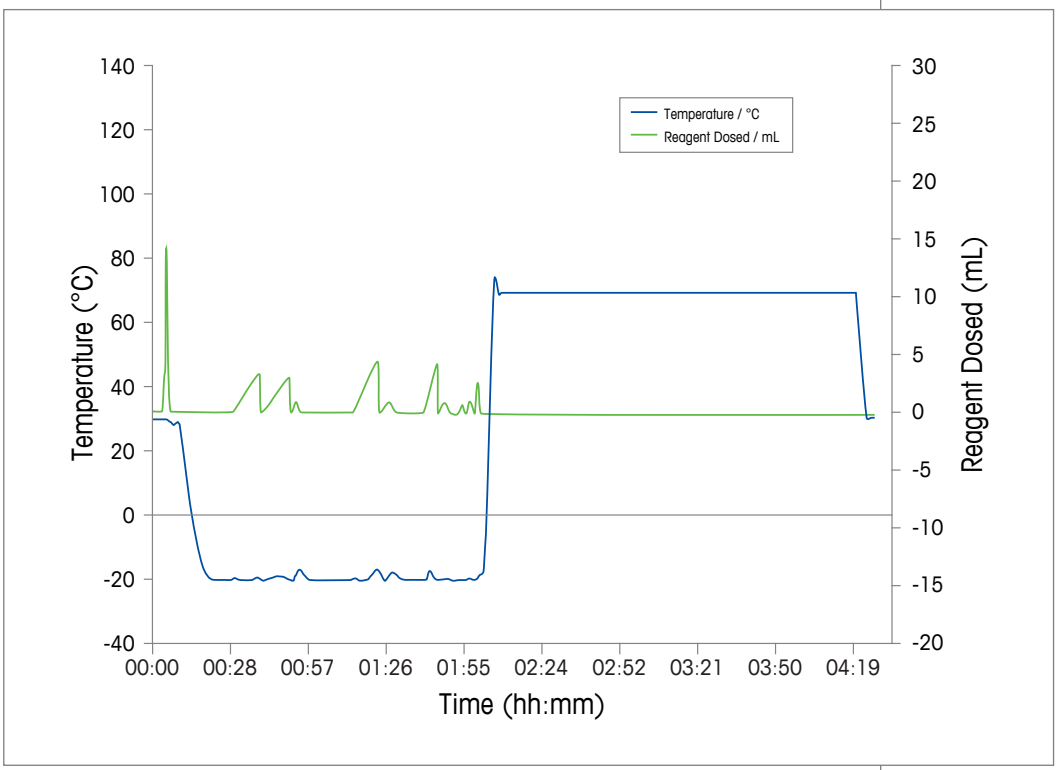


Figure 2. Reagent addition durning the reaction. All additions were executed by the synthesis workstation.

Repeating a Synthesis is Not as Easy as it Should be

In the example, the synthesis is completed, and the desired compound has been made to the purity and yield desired. In other words, the ideal outcome has been achieved. But can it be repeated, to the exact same outcome, the following day or week? This should be a simple task. However, this is not always the case, especially with reactions where the mechanism is dependent on a number of factors.

It is now possible to repeat the synthesis from a previous experiment with enhanced confidence that the outcome will be the same as it was before. The synthesis workstation recorded everything that was done in the previous experiment. Recreating the synthesis is now a simple matter of cloning the previously successful experiment and pressing 'go'. The chemist can be confident that the exact same conditions will be applied to this synthesis as to the previous one.

All chemists have experienced two apparently identical experiments producing a different outcome. Chemistry is like that, but surely there must be a reason? The synthesis workstation records data during the course of a synthesis which provides insight into the experimental result. This data, combined with a recorded recipe, and crucially when these steps were taken, means a chemist can go back and directly compare two experiments, side by side. If one works, and the other doesn't, they can be directly compared to identify what changed between the two, and the successful recipe is revealed. In other words, consistent data collection means a chemist can determine precisely what was done so it can be repeated.

Time	Name
hhh:mm:ss	
0:02:50	DIOL+15ML DRY ACN
0:06:55	START STIRRING
0:07:51	STIRRING UNDER AR
0:08:53	COOLING AT -20 C
0:25:54	DOSE 3;5ML ANHYDR
0:34:06	WHITE PRECIPITATE
0:39:55	3ML DRY ACN
0:40:29	WASH DOSING TUBE
0:44:37	LIGHT YELLOW COL
0:45:59	AGAIN HOMOGENOUS
0:51:46	3ML ACN TUBE WASH
1:11:47	DOSING DEVICE WAS WASHED
1:13:19	4;5ML DIEA DOSING
1:25:40	3X1ML ACN TUBE WASH
1:25:52	WASH
1:31:03	STIRRING 10MIN
1:40:51	4;5ML DIEA DOSING
1:44:10	YELLOWISH COLOR DISAPPEARING
1:47:04	3X1ML ACN WASH THE DOSING TUBE
1:54:11	0;8ML AMINE DOSE
1:56:27	3X1ML ACN WASH
2:01:44	3ML ACN TUBE WASH
2:11:37	YELLOW COLOR
3:15:17	DARKYELLOW COLOR
4:21:03	R TIME EXPIRED
4:27:11	ORANE COLOR

Figure 3. List of actions from the experiment.

"The EasyMax™ system provides us with a simple, reliable system that is the workhorse of our lab."

Anthony M. DiJulio,
Scientist Particle Engineering,
Novartis Pharmaceuticals Corp.,
NJ, USA

Conclusion

Chemists are continually developing new techniques to perform organic syntheses. One of those new techniques is the synthesis workstation.

Using a synthesis workstation, ice (both water ice and dry ice) and oil baths are eliminated, resulting in more consistent temperature control, which results in better chemistry. These workstations provide a simple way to heat and cool a reaction that is much simpler and more reliable than a traditional ice or oil bath. Chemists are able to focus on chemistry, not on equipment.

Recording everything means chemists can reproduce everything that was done before. This means a successful synthesis can be repeated with one click, or passed to another colleague to repeat anywhere in the World. The data recording also means any key reaction event is never missed, whether the chemist is present or not.

The synthesis workstation allows reactions to be run unattended, safely around the clock and chemists no longer have to supervise lengthy hold times.

EasyMax™ and OptiMax™: Replacing the Round Bottom Flask

EasyMax™ and OptiMax™ synthesis workstations eliminate the need to use heating mantles, oil and ice baths and cryostats. With no training requirement, EasyMax™ is fast and easy to set up, making users immediately productive. The touch screen is used to change conditions, and program a few steps ahead.

Reactions can be safely run unattended, day or night. The systems capture experimental data to deliver an enhanced understanding of the reaction under investigation, leading to faster reaction optimization. Every reaction event is captured, and experiments are easily compared and repeated.

EasyMax™

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Internet: http://www.mt.com/autochem

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We are online at the METTLER TOLEDO website (www.mt.com/autochem), where you can find additional detailed information on our products and applications – including an extensive list of upcoming and on-demand webinars.

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