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GREEN CHEMISTRY

Speedy synthesis in a spray

> “Some want more information on the mechanism, and a few — bless them — simply don’t believe what I say!”

Confining chemical reagents in small solvent droplets is known to result in notable enhancements in reaction rate. This observation has naturally attracted the attention of synthetic chemists, but the small scale of the reactions described and the large amounts of solvent used have meant that there have been few practical applications of the technique. Now, Graham Cooks and co-workers from Purdue University have described a spray reactor system that enables synthesis in high yield, at a production rate on the order of multiple grams per hour, and allows solvent to be recycled.

The Cooks group has been investigating the rate enhancement phenomenon for some time. “We initially observed increased reaction rates when performing analyte derivatization experiments for desorption electrospray ionization spectrometry (DESI),” says Cooks. “Reagents were added to the spray solvent, and the resulting reactions were frequently observed to occur at rates thousands of times faster than the corresponding bulk reactions.”

The group studied their system using four different reactions: a Claisen–Schmidt reaction, a Schiff base formation, a Katritzky reaction and a Suzuki reaction. “We chose these reactions because they cover a variety of reaction types, but all fit our criterion of facilitating reaction monitoring by mass spectrometry because both the reactants and products are easily ionized,” explains Cooks.

The reagents are only in the microdroplet spray form for a limited time, so Cooks and co-workers developed a system whereby the sprayed droplets are collected as a thin film in which the reaction can continue. The rates of reaction in the film are somewhat slower than in microdroplets but still higher than in bulk, and importantly this enables extended reaction times and thus higher reaction conversions.

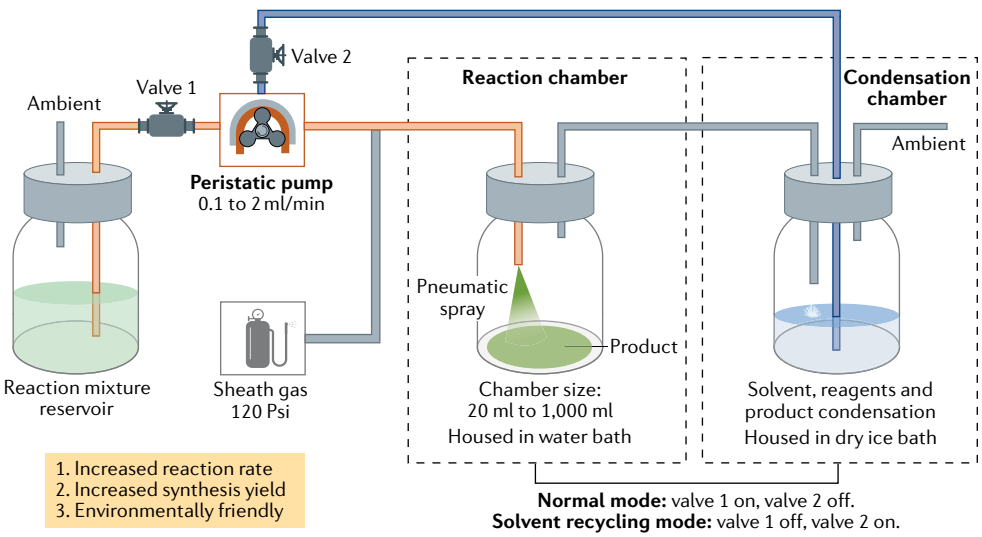
The rates of the four reactions studied were found to be between 15 and ~7,700 times faster in microdroplets and thin films than bulk reactions using the same initial concentrations. The improved performance of reactions in thin films and droplets is not entirely clear but has been attributed to a variety of effects that operate on this scale, not least the rapid transport of reagents within small droplets. The large ratio of surface area to volume is also important because reagents may be exposed to conditions of extreme pH and dipole effects that dominate at the interface but whose contributions to overall rate are insignificant in bulk. The largest acceleration was observed for the Claisen–Schmidt reaction, an acid- or base-promoted reaction that likely benefits from the pH extremes. The smallest acceleration is for the Suzuki reaction, in which the rate is highly dependent on catalyst loading. In this case, the reaction can still benefit from rapid mass transport.

Comparing the yields of bulk and sprayed reactions over time reveals that whereas bulk reactions continue slowly, the sprayed reactions proceed rapidly but give yields that plateau after several minutes. For the most rapid reactions, plateauing occurs at maximum reaction yield. For slower reactions, the addition of a solvent recycling system improves both yield and the green credentials of the reaction system.

Asked how easy such a system is to set up, Cooks is very straight: “I’ve been doing this chemistry and talking about it for 10 years, but I’m yet to see anyone run out of the lecture room in order to set up the experiment that afternoon. Some want more information on the mechanism, and a few — bless them — simply don’t believe what I say!”

With the support of DARPA, Cooks’ team are building a system for combined reaction screening and bioactivity monitoring. “We’re currently able to perform about 6,000 reactions per hour,” he says. The team also hope to apply their system to multistep reaction sequences.

Stephen G. Davey



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ORIGINAL ARTICLE Nie, H. et al. High-yield gram-scale organic synthesis using accelerated microdroplet/thin film reactions with solvent recycling. *Chem. Sci.* https://doi.org/10.1039/c9sc06265c (2020)