NEW ALTERNATIVE TO BEAD SYNTHESIS

Precipitons ease separation of products from solution-based reaction mixtures

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Researchers at the University of Pittsburgh have developed a convenient new way to separate products from reaction mixtures produced in solution-phase organic synthesis. The method, in which reactants are drawn into and precipitated out of solution by attached auxiliary groups called "precipitons," was devised to permit greater use of solution-phase synthesis as an alternative to solid-phase organic synthesis (SPOS).

In SPOS, reactants are attached to solid-phase support beads to ease recovery of reaction products created from those reactants in subsequent chemical reactions. The SPOS approach is popular because an excess of reagents can be used to increase product yields and products can be isolated by simple filtration. But it has significant drawbacks—SPOS reactions are often slower than corresponding homogeneous solution reactions, development and optimization of reagent immobilization procedures can be time-consuming, and beads can interfere with reactions and reaction monitoring.

As a result of these difficulties, researchers have developed a series of SPOS replacement techniques. These techniques make it possible to carry out reactions in a homogeneous solution but still recover products fairly easily.

Now, graduate students Todd Bosanac and Jaemoon Yang and chemistry professor Craig S. Wilcox at the department of chemistry and the Combinatorial Chemistry Center of the University of Pittsburgh have extended the repertoire of such techniques by developing a new method based on precipitons. These molecular fragments are added to synthetic starting materials and then isomerized after the reaction to ease phase transfer and then convenient precipitation of attached products [Angew. Chem. Int. Ed., 40, 1875 (2001)].

In their study, the researchers synthesized stilbene-based precipitons that adopt two stereoisomeric forms—one freely soluble in common organic solvents and the other virtually insoluble. The precipitons, in their soluble form, were attached to alkenoates. The alkenoates were then treated with nitrile oxides in ether, yielding isoxazoline products.

BY ISOMERIZING the precipitons chemically after the reaction was complete, Wilcox and coworkers were able to isolate the precipiton-bound isoxazolines in good yield and at high purity by filtration. They refer to such a structural change leading to phase separation as a "tactical isomerization." They then cleave the isoxazoline products from the precipiton groups.

According to Wilcox and coworkers, advantages of the precipiton approach include the ability to perform reactions in homogenous solution and the ability to monitor the reactions easily by standard analytical methods, such as thin-layer and liquid chromatography. In addition, loading capacities for the precipiton phase tags are high, little solvent is used during the isolation stage of the synthesis, the technique is applicable to both large- and small-scale syntheses, and it potentially can be automated.

A number of other SPOS alternatives have been developed in the past few years. Most of these techniques permit reactants to be in organic solution for a reaction and then transfer the corresponding products into a different phase for separation.

One of the first was a soluble polymer-supported organic synthesis technique devised by chemistry professor Kim D. Janda and coworkers at Scripps Research Institute [Proc. Natl. Acad. Sci. USA, 92, 6419 (1995)]. In this approach, syntheses are carried out on soluble polymers, such as polyethylene glycol. The polymers, and attached reaction products, can then be precipitated out of solution for purification purposes by adding other solvents.

Another SPOS alternative is fluororous synthesis, developed by chemistry professor Dennis P. Curran and coworkers at Pitt [Science, 275, 823 (1997)]. In this technique, synthetic starting materials are tagged with fluororous (polyfluorinated) reagents and put through a series of reaction steps in solution. Fluorous-tagged synthetic products are separated by partitioning into fluororous solvents, and the fluororous group is removed to generate pure products.
Arnold Schwarzenegger as chemistry professor Craig Wilcox—a sure box office smash."

However, Curran adds, "I tried to get Craig to go for 'precipitator.' It's less chemical, but it would be much better when the movie comes along: 'The Precipitator,' starring..."

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STILBENE PRECIPITON The cis form is freely soluble in common organic solvents, whereas the trans form is virtually insoluble.

"With all of these techniques, you have homogeneous conditions and thus the chance for better overall kinetics that mirror solution-phase synthesis," Janda notes. "In addition, you have a method to quickly purify your product."

Janda calls the precipiton study "a clever piece of work." Major advantages of the method, he says, are "high loading and simplicity of the tag handle." But a disadvantage is "the reactivity of the phase tag. It has a double bond, and I don't think it can be easily recycled."

In addition, Janda says, "the time to change precipiton phases is a bit long and not that simple—that is, it takes some manipulation." Precipitons may not be capable of solubilizing high-molecular-weight reactants. "And I don't know how readily the method could be automated—but if there is a will, then there is an engineer who could do this," Janda says.

Wilcox replies, "We anticipated the need for recycling and discussed that in our paper." Furthermore, he says, "we already have faster methods for tactical isomerization, and we envision a toolbox of precipitons that can be used to cover a large variety of reaction conditions."

LEY COMMENTS that "the idea of purification by changing the structure of a tag is clever and, I think, new." However, Ley doesn't believe the precipiton approach "is particularly cheap or easier than existing methods." Also, he says, "I do not think the method is amenable to multistep synthesis, especially as once the isomerization has occurred, the product is insoluble and re-isomerization to a soluble material is not yet feasible. Before the technique becomes really useful, these issues would need to be addressed. Nevertheless, the method is a useful contribution."

But Curran, Wilcox's colleague at Pitt, says the precipiton concept represents "a very significant new direction" in the field. "I foresee, for example, that precipitons could well be useful for large-scale synthesis. So precipitons could be the advance that moves phase tagging from the discovery platform to the process chemistry platform."

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