Electrochemistry breakthrough simplifies creation of coveted molecules for drugs, electronics

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A new chemistry method from scientists at Scripps Research in La Jolla, California, greatly simplifies the creation of an important class of compounds called hindered ethers, which are integral to many drugs and commercial products. Hindered ethers are often coveted for their special properties, but until now have required laborious methods to synthesize.

The new method, reported in *Nature*, may also help bring "electrochemistry" into the mainstream of modern medicinal chemistry.

Electrochemistry involves passing a current through a compound in liquid solution to generate a key reactive component. Traditional electrochemistry techniques are often very limited in their scope, but the Scripps Research scientists demonstrated the broad versatility of their technique by showing that it can perform faster, higher-yield syntheses of dozens of hindered ethers used in products today.

"These are compounds that historically have required more than a dozen steps and more than a week of work to synthesize using standard methods," says Phil Baran, Ph.D., the Darlene Shiley Chair in Chemistry at Scripps Research and senior author of the study. "With our method, the compounds can be made in just a few steps—often in less than a day—and for that reason, drug companies that know of this new method already have started using it."

Hindered ethers are particularly prized as structures in medicines because they can be made to powerfully resist enzymes in the human body that would otherwise degrade the drug molecules quickly. Yet the standard approach to creating ethers, a 168-year-old process known as the "Williamson ether synthesis," becomes unwieldy when the desired ether includes bulky side-groups of atoms. These atoms can hinder the ether's reactivity (thus, the term "hindered").

Baran and his team in recent years began exploring new electrochemical methods with the hope of improving upon this old, yet somewhat neglected, realm of chemistry to create valuable molecules that were otherwise hard or impossible to make. To address the problem of synthesizing hindered ethers, they investigated a little-used electrochemical method called the Hofer-Moest reaction, first published in 1902.

This method can generate an important reactive intermediate molecule known as a carbocation ("carbo-cat-ion") needed for ether synthesis from an inexpensive carboxylic acid. However, this method requires a high electric current and an expensive setup, including platinum electrodes. These and other factors have severely limited this reaction's utility. Over the course of hundreds of experiments, Baran and his team developed their own easier and more versatile technique, which uses a low electric current compatible with the simplest electrochemistry equipment, a cheap carbon electrode, and improved solvents and electrolytes.

In their paper, Baran and his colleagues describe more than 80 examples of hindered ethers they were able to create using the new method. These include:

- A key building-block of a potential cancer drug, which the team synthesized in just 15 hours with a yield of 51 percent, compared

with six days and 3.4 percent yield for the standard method;
- A key building-block of a potential diabetes drug, which the team synthesized in three hours in a single step, compared with 2.5 days and five steps for the previous method;
- A key building-block of a potential HIV drug, which the team synthesized cheaply with one step in three hours, compared with six steps and two days, with a requirement for expensive reaction materials, for the previous method;
- A key building-block of liquid crystals used in LCD monitors, which the team made in one step in three hours, compared with four steps in two days for the previous method. LCD technology is widely used in products such as laptops, flat-screen TVs, digital cameras and watches.

In a selection of these and eight other real-world examples, the team found that the new method enabled an average yield of 43 percent, average step count of 1.5 and average time of 9.8 hours, compared with averages of 19 percent, 6.3 steps and about 100 hours using previous methods.

"These are compounds that we know people care about and are making, so we expect this method to have a real impact," Baran says.

He notes that the new method can be used at small or modest scales—for example, for the exploratory chemistry of drug discovery—but also for large-scale chemical production. Additionally, the method makes it easy for medicinal chemists to generate sets or "libraries" of closely related compounds; they can use the same basic setup and starting compound, and simply vary some of the reaction ingredients. The study was a collaboration with the laboratory of Donna Blackmond, Ph.D., professor and co-chair of chemistry at Scripps Research.

"The contributions from Donna and her students were critical in helping

us develop this chemistry," Baran says. "They elucidated a molecular understanding of each of the processes occurring in the reaction flask, so we could rationally optimize the new method."

Baran and his team are now exploring other potential applications of their method.

"Its ability to generate highly reactive carbocations under mild conditions suggests that we might be able to use it to make other classes of molecules that were previously inaccessible," Baran says.

The authors of the study, "Hindered Dialkyl Ether Synthesis with Electrogenerated Carbocations," include Jinbao Xiang, Ming Shang, Yu Kawamata, Helena Lundberg, Solomon Reisberg, Miao Chen, Pavel Mykhailiuk, Donna Blackmond, and Phil Baran, all of Scripps Research; Gregory Beutner of Bristol-Myers Squibb; and Michael Collins, Alyn Davies, Matthew Del Bel, Gary Gallego, Jillian Spangler, Jeremy Starr, and Shouliang Yang of Pfizer.

More information: Jinbao Xiang et al, Hindered dialkyl ether synthesis with electrogenerated carbocations, *Nature* (2019). DOI: 10.1038/s41586-019-1539-y

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