Inventive technique transforms a common reagent into a multifunctional tool for pharmaceutical synthesis

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Calcium carbide (CaC_2) is a simple molecule used worldwide to produce industrial-scale quantities of the fuel known as acetylene gas (see image). Chemists have found ways to generate CaC_2 from sustainable biomass resources, making this compound even more attractive as a fundamental 'building block' for organic chemistry. Direct use of CaC_2 as a synthetic reagent, however, is rare because it has poor solubility in most organic solvents.

Yugen Zhang and co-workers from the A*STAR Institute of Bioengineering and Nanotechnology, Singapore, are now set to resolve this solubility problem. They have developed a new protocol that uses CaC_2, a copper catalyst and a dash of water to produce an important synthetic intermediate for pharmaceutical compounds1.

Enaminones are organic compounds that link amines and carbonyl chemical groups through an unsaturated carbon double bond. This arrangement gives enaminones both electron-repelling (nucleophilic) and electron-attracting (electrophilic) capabilities, which are useful during the synthesis of complex drugs that mimic natural biological products. Typically, however, chemists take multiple steps to construct these multifunctional reagents.

Zhang and co-workers recently developed a catalytic route that turns CaC_2 into propargylamines—molecules with acetylene, alkyl and amine

groups—by dissolving it with highly polar organic solvents. Under certain conditions, the team noticed that small amounts of enaminones were also produced—a finding that suggested liquid acetylide ions (C22-) could act as a bridge to connect nucleophilic and electrophilic chemicals in a single reaction pot.

When the team investigated a three-way catalytic coupling between acetylide ions, an amine, and an aldehyde, they saw an extraordinary dependence on solvent choice. Acetonitrile, a nitrogen-bearing solvent, yielded predominantly propargylamines, while dimethylformamide (DMF)—a solvent that contains aldehyde and amine groups—produced the enaminone targets. Intriguingly, a fractional 1% addition of water to the DMF solvent rapidly sped up enaminone production.

Mechanistic experiments revealed that water molecules, besides improving the solubility of CaC_2, also acted as a proton source that helped to generate enaminones from a catalytic copper complex. Furthermore, the team discovered that they could also fine-tune their synthesis by changing the size of their starting materials: bulky amine reagents tended to provide the kinetic conditions needed to bridge nucleophilic and electrophilic units.

Zhang notes that the cost-effectiveness and efficiency of these findings could make researchers rethink the role of CaC_2 in modern organic synthesis. "Chemistry is extremely versatile and we can expect surprising results," he says. "Just because a reaction has not yet occurred does not mean that it will never happen in the future."

More information: Yu, D., Sum, Y. N., Ean, A. C. C., Chin, M. P. & Zhang, Y. Acetylide ion (C22-) as a synthon to link electrophiles and nucleophiles: A simple method for enaminone synthesis. *Angewandte Chemie International Edition* 52, 5125–5128 (2013). dx.doi.org/10.1002/anie.201301019