Safe, inexpensive iron catalysts provide a 'greener' alternative to typical pharmaceutical production methods

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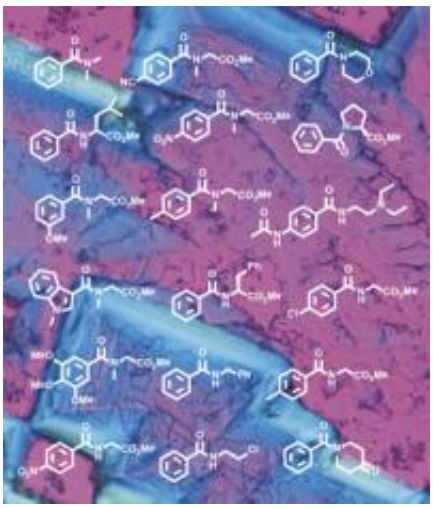

A polarized light micrograph of iron(II) sulfate crystals (background) that can catalyze formation of amide compounds (white structures) cheaply and efficiently. Credit (Background)Comstock Images/Thinkstock; Credit: (Foreground)2013 A*STAR Institute of Chemical and Engineering Sciences

More than one-quarter of all known pharmaceuticals contain the chemical group known as amides: carboxylic acid derivatives derived from ammonia or amines. Most methods for synthesizing amides, however, are inefficient and use hazardous reagents. New work from Anqi Chen and co-workers at the A*STAR Institute of Chemical and Engineering Sciences in Singapore promises to make amide chemistry

more economical and sustainable than before. The team has uncovered a way to convert aldehydes and amine salts into amides using iron(II) sulfate—a harmless, inexpensive substance as the catalyst to perform this transformation efficiently and with little waste.

Most alternative methods to produce amide molecules use expensive noble metal catalysts such as palladium and ruthenium, which are incompatible with industrial demands for cost-efficiency. Funded by a GlaxoSmithKline (GSK)–Singapore Economic Development Board (EDB) endowment on sustainable drug manufacturing, the researchers investigated a different approach known as 'direct oxidative amidation'. This method couples an aldehyde and an amine salt in the presence of a catalyst and an oxidant, generating an amide in one step.

Nontoxic and cheap catalysts with sufficient chemical activity for amide transformation are hard to find. To identify an efficient and inexpensive catalyst, the team screened a range of iron compounds and discovered that iron(II) sulfate (see image), a supplement for anemia that costs less than a dollar per kilogram, has strong potential to catalyze amide formation from aldehydes with amine salts.

Apart from the environmentally benign iron catalyst, the transformation uses an inexpensive oxidant known as tert-butyl hydroperoxide and very cheap calcium carbonate, the main composition of limestone, as a base. By combining these inexpensive ingredients together, the researchers achieved excellent amide yields under conditions convenient for both laboratory and industrial operations.

Further experiments revealed the versatility of this amide synthesis. A range of amine salts and aldehydes with different structural and electronic features could be transformed into amides with good-to-excellent yields. Importantly, salts derived from natural amino acids such as valine and proline also underwent oxidative amidation without

disrupting their chirality or 'handedness'—a critical structural phenomenon for drug molecules and peptides.

The team demonstrated the potential of this iron-catalyzed amidation for drug manufacturing by synthesizing the antiarrhythmic drug N-acetylprocainamide in a one-step procedure that is more efficient than previous multiple-step routes. "This environmentally benign method has significant advantages over conventional techniques," says Chen, "and we intend to identify pharmaceutical targets where this promising method could bring about significant cost-savings and improved sustainability."

More information: Ghosh, S. C., Ngiam, J. S. Y., Chai, C. L. L., Seayad, A. M., Dang, T. T. & Chen, A. Iron-catalyzed efficient synthesis of amides from aldehydes and amine hydrochloride salts. *Advanced Synthesis & Catalysis* 354, 1407–1412 (2012). dx.doi.org/10.1002/adsc.201200020

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