Nature Reviews Chemistry | https://doi.org/10.1038/s41570-019-0102-6 | Published online 1 May 2019

FLOW CHEMISTRY

Seven steps, no stops

Synthesis in flow offers some key advantages over batch processes. Precise control of reaction conditions, such as reaction time and temperature, can lead to greater selectivity, while also enabling the use of reactions that may prove challenging in batch mode, such as those that involve highly reactive or short-lived intermediates. Despite this, syntheses that employ flow conditions rarely exceed two steps before offline purification. Now, writing in *Angewandte Chemie*, Grace Russell and Tim Jamison from the Massachusetts Institute of Technology describe a seven step continuous flow synthesis of the antibacterial drug linezolid (Zyvox).

Linezolid is used as a last line of defence against multidrug-resistant Gram-positive bacterial infections, including drug-resistant tuberculosis. As a result, it is included on the World Health Organization's list of essential medicines. Russell and Jamison's synthesis of this important drug is achieved in just seven continuous steps with no stops to purify intermediates or even pauses to exchange solvents.

The key, convergent step in the designed synthesis is the ring opening of an epoxide with an aniline. These two key intermediates were themselves prepared in flow before combination.

The aniline was prepared by a nucleophilic aromatic substitution reaction involving 1,2-difluoro-4-nitrobenzene and morpholine. The resulting nitrobenzene was then reduced to the aniline by hydrogenation over a palladium catalyst. The solvent system for this reaction was optimized to enable both a rapid S_NAr reaction while keeping all the reactants and products in solution and for compatibility with the reduction catalyst.

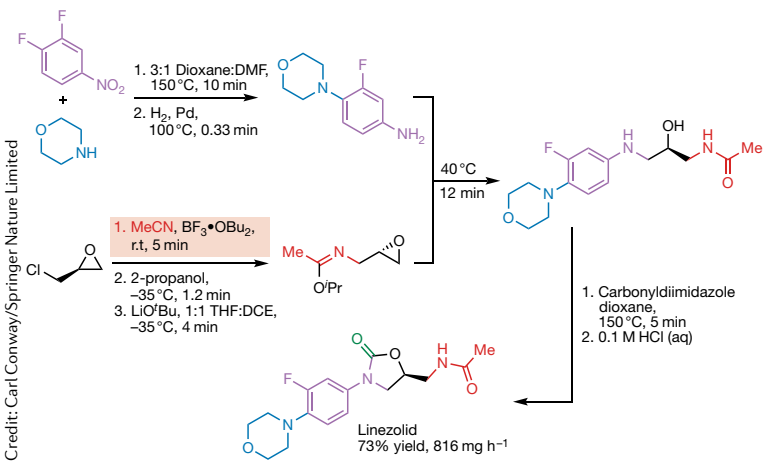
In a second stream, a Lewis-acid-mediated ring-opening of (+)-epichlorohydrin with acetonitrile begins the epoxide synthesis. While this had been considered in previous batch syntheses, the approach had been abandoned owing to competitive formation of an oxazoline byproduct — a side-reaction that can be suppressed under flow conditions. Other optimizations to the procedure included the use of boron trifluoride dibutyl etherate (instead of the more common diethyl etherate) and quenching with isopropanol in place of water to avoid the formation of insoluble side-products. Treatment with lithium tert-butoxide led to the formation of an imidate-masked amino epoxide intermediate.

Combining the aniline and epoxide intermediates led to the desired epoxide ring opening with concomitant hydrolysis of the imidate to an amide. Russell and Jamison propose that it is the water byproduct from the earlier nitroaromatic to aniline reduction that is responsible for this hydrolysis.

Both the aniline intermediate and the amino alcohol product of epoxide ring opening were found to be sensitive to oxidation, but once again flow chemistry helps, because these intermediates can be generated and consumed rapidly in the process.

The synthesis was completed by reaction of the amino alcohol with carbonyldiimidazole to generate the oxazolidinone product, which was then purified offline. The complete procedure enables the production of linezolid in an impressive 73% yield over 7 steps (an average of just over 95% per step) and at a rate approaching one gram per hour.

Stephen G. Davey



Credit: Carl Conway/Springer Nature Limited

ORIGINAL ARTICLE Russell, M. G. & Jamison, T. F. Seven-step continuous flow synthesis of linezolid without intermediate purification. *Angew. Chem. Int. Ed.* https://doi.org/10.1002/anie.201901814 (2019)