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A Microreactor Strategy for the Synthesis of Tetrazoles

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The broad application of the tetrazole scaffold in different fields, such as general and coordination chemistry, material science, microbiological and medicinal chemistry in recent years demands robust and safe methods for their preparation on production scale. From the many developed methods for the synthesis of the tetrazole nucleus, the [3+2] cycloaddition of an azide partner to a nitrile is by far the most simple, atom efficient and inexpensive strategy. However, hydrazoic acid (HN_3) and its salts are extremely toxic and many metal azides and hydrazoic acid itself are extremely explosive.

Great advances in the synthesis of substituted tetrazoles were achieved since the first reports dating back to the mid 1950's. Today, a variety of protocols are available that allow the synthesis of tetrazoles from azides and nitriles. However, none of these routes are suitable for a genuinely scalable production route, as these batch protocols often involve toxic/explosive intermediates or explosive sublimates, the use of toxic and/or expensive reagents or stoichiometric amounts of inorganic salts, in addition to long reaction times.

Here we present a simple, safe, fast and inexpensive protocol for the synthesis of 5-substituted tetrazoles under continuous flow conditions. We have discovered that the reaction can be cleanly performed using in-situ formed hydrazoic acid at very high temperatures and comparatively short reaction times using a process intensification regime to yield tetrazole products in excellent yields. The details of our microreactor strategy will be discussed.