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SYNTHETIC METHODOLOGY

Labelling of bioactive azaarenes

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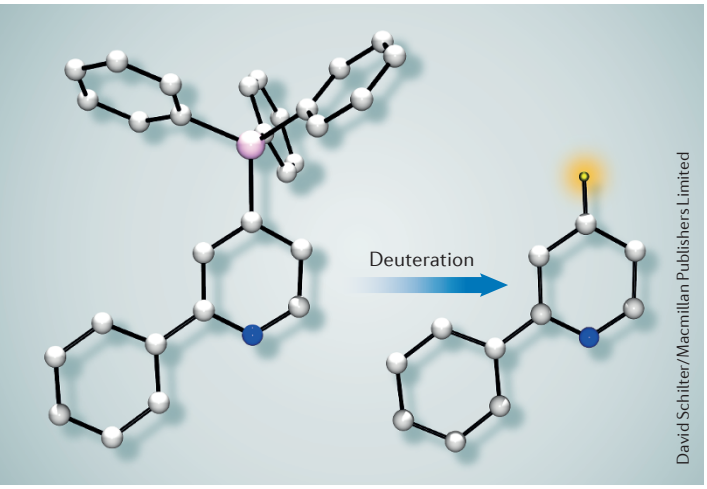
Preparing isotopically labelled bioactive molecules is a useful means of assessing safety, distribution and metabolism. Moreover, labelled compounds are increasingly becoming important pharmaceuticals in their own right. The difference in mass between a hydrogen atom and its heavier deuterium and tritium isotopes has important consequences: a molecule whose metabolic pathway involves reactions at a C–H bond can potentially be stabilised in vivo by substituting a heavier isotope at that position. But the selective and efficient installation of hydrogen isotopes in pharmaceutically important structures such as nitrogen-containing heteroarenes can be challenging. Writing in the *Journal of the American Chemical Society*, a team led by Andy McNally, in collaboration with researchers at Merck, describes a new approach to the selective labelling of pyridines and diazines with deuterium or tritium. Their method uses common reagents found in most synthesis laboratories and is compatible with a range of bioactive molecules. "The process is remarkably broad and selective, even in the complex structures encountered in pharmaceutical compounds," says McNally.



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The new method builds on the group's existing approach to phosphonium-appended heteroarenes. McNally's group has previously shown that a phosphonium can readily be introduced at the 4-position of a pyridine using triphenylphosphine and triflic anhydride. The resulting salts are isolable intermediates that are useful in a variety of reactions, including classic cross-couplings. But when the salts are treated with base, the C–P bond undergoes cleavage, regenerating the original heteroarene in a reaction that is thought to proceed via an anionic intermediate. This often undesirable process is key to the new labelling procedure. "Ironically, the method uses a reaction pathway that would normally be regarded as problematic," comments McNally. "We realised that if an acidic isotope source such as isotopically labelled water or methanol was present, then the anionic intermediate could be intercepted to make C–D and C–T bonds."

The team found that simply stirring the phosphonium salts with a base in deuterated water or deuterated methanol allows a wide range of pyridines and diazines to be selectively labelled at the 4-position. Likewise, the use of CH_3OT — obtained from T_2 gas — enables clean tritation of a pyridine at the 4-position. Beyond simple fragments that demonstrate the useful functional group tolerance of this method, the authors synthesized labelled analogues of a dozen known bioactive molecules.

Pyridines and diazines have proven challenging for existing methods, hence the new approach serves as a useful complement to the growing suite of modern isotopic labelling methods. Likewise, the high regioselectivity of this method for the 4-position means we have an strategy that is orthogonal to recently reported catalytic methods which selectively label other aromatic protons or C(sp^3)–H sites. Moving beyond the installation of hydrogen isotopes, phosphonium salts may see use as general reagents for labelling heteroarenes with heavier atoms such as carbon and fluorine isotopes.

It can be expected that this method will help provide the labelled materials necessary to characterize the in vivo behaviour and safety profile of new pharmaceuticals, and indeed to the synthesis of new drugs that rely on isotopic labelling for metabolic stability. Such methods will only grow in importance for human health, with the first commercial drug incorporating deuterium — deutetrabenazine — having been approved by the US Food and Drug Administration in 2017. "Suddenly, you begin to realize that new ways of installing hydrogen isotopes into organic molecules can have a genuine impact in the real world," concludes McNally.

Andrew Bissette, Associate Editor,
Communications Chemistry

ORIGINAL ARTICLE Koniarczyk, J. et al. A general strategy for site-selective incorporation of deuterium and tritium into pyridines, diazines and pharmaceuticals. *J. Am. Chem. Soc.* https://doi.org/10.1021/jacs.7b11710 (2018)
FURTHER READING Loh, Y. Y. et al. Photoredox-catalyzed deuteration and tritiation of pharmaceutical compounds. *Science* **358**, 1182–1187 (2017)