Simple way to add nitrogen to drugs

Synthesis abolishes need for protecting groups

US researchers have discovered a simple, one-pot, scaleable way to synthesise aziridines – three-membered rings that are important building blocks for introducing nitrogen into more complex molecules, including medicinal drugs.

Current routes for aziridine synthesis typically require a protecting group on the nitrogen atom that provides stability to the molecule. However, this N-protecting group must then be removed in order to use aziridines as building blocks and this removal involves harsh reaction conditions, which often damages the ring structure, limiting its use.

Now, a direct method for preparing N–H and N–Me aziridines from alkenes under mild conditions has been developed that avoids the need for an N-protecting group.

'The surprising synthetic and mechanistic results presented in our paper constitute a paradigm shift and will be of considerable interest not only to synthetic and medicinal chemists but also to the theoretical, structural and organometallic communities,' says László Kürti, a co-author of the work at the University of Texas Southwestern Medical Center.

The aziridination method involves the reaction of an alkene with the aminating agents DPH (dinitrophenyl-hydroxylamine) or *N*-methyl–DPH in the presence of a rhodium catalyst, which produces N–H or N–Me aziridines at ambient temperature. 'As often happens, the yields were initially poor, but were gradually optimised by a systematic investigation of the reaction parameters, especially the metal catalyst and its ligands,' Kürti explains.

'The stereospecificity of this process was especially surprising – the literature predicts that in order to make a single metal nitrene, the N atom must have a strongly electron-withdrawing [N-protecting] group,' says Kürti. 'Clearly, we had to have a very interesting mechanism in order to observe a high degree of stereospecificity.'

'This important advance not only allows stereospecific access to versatile N–H aziridines from a wide range of unactivated substrates, it does so under mild conditions with simple reagents,' comments James Bull, who investigates aziridine synthesis at Imperial College London, UK. 'Generating the reactive nitrene catalytically and without requiring an additional base or oxidant is crucial, allowing extremely sensitive functional groups to be tolerated. As a result this method is likely to provide much improved access to valuable synthetic intermediates.'

However, the team recognises the reaction is limited by not being able to selectively produce a particular mirror image of the molecule. 'An enantioselective version of this transformation would be desirable but currently we do not have a suitable chiral catalyst that produces practical levels of asymmetric induction,' says Kürti. 'The development of new chiral ligands and catalysts is a major focus of our collaborative effort.' *James Urquhart*

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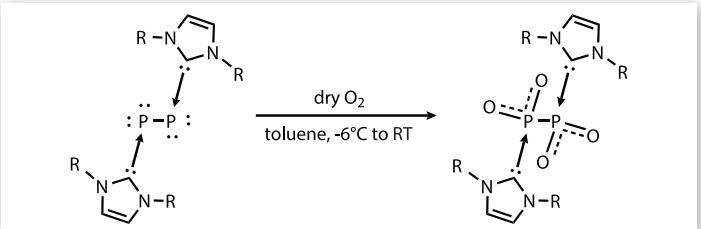
First route to diphosphorus tetroxide

Backdoor approach helps create elusive molecule

Researchers from the University of Georgia, US, are the first to synthesise stable diphosphorus tetroxide, the long sought-after phosphorus analogue of N_2O_4. What's more, they performed the feat at room temperature.

Despite hailing from the same pnictogen family, the properties of phosphorus and nitrogen couldn't be more different. As one of the most ubiquitous gases in nature, nitrogen can readily be isolated as a series of oxides. Diphosphorus (P_2), on the other hand, is transient and its oxide relative of N_2O_4 is highly reactive. Until now, this has meant that studying diphosphorus tetroxide was limited to cryogenic temperatures, making it an extremely elusive compound.

Explaining how they were able to isolate P_2O_4, team leader Gregory Robinson described their 'backdoor' approach based on earlier work on carbene-stabilisation of small, highly reactive, main group molecules. Using the organic base *N*-heterocyclic carbene, the team managed to stabilise the diphosphorus molecule. 'With carbene-stabilised diphosphorus in hand, we simply utilise molecular oxygen as an oxidant,' he explains. 'Stabilised diphosphorus simply splits molecular oxygen yielding a stable molecule containing diphosphorus tetroxide.'



After stabilising diphosphorus using a pair of carbenes the oxide was created simply by adding molecular oxygen

On characterising the compound, the results turned out to be something of a surprise. While computation predicts the most energetically favourable structure is an oxo-bridged O_2POPO structure, the team found that they had stabilised the $O_2P–PO_2$ isomer instead.

More importantly, they also found the carbene-stabilised diphosphorus tetroxide represents the first example of a phosphorus oxide exhibiting Lewis acid behaviour. 'The fact that diphosphorus tetroxide can be induced to behave as a Lewis acid further confirms that Lewis bases, such as *N*-heterocyclic carbenes, are versatile tools that may help chemists access the largely unexplored chemistry of phosphorus oxides, and possibly other main group oxides,' Robinson adds.

Stephen Liddle, at the University of Nottingham, UK, believes this demonstrates a universal lesson when working with reactive species, as it overturns preconceptions about the possibility of such molecular fractions simply by careful selection of the stabilising species. 'This is an elegant kinetic trapping technique in which they have made a species that can be isolated under ambient conditions. This means that the synthetic chemist can put it in a jar and do chemistry with it,' he adds. 'By inverting the Lewis character, it demonstrates that you never know what new chemistry can come out of it'.

While the question of potential applications remains unanswered, Robinson and his team are continuing to study the reactivity of the molecule. *Caryl Richards*

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