

## The Synthesis of $\alpha$ -Azidoesters and Geminal Triazides

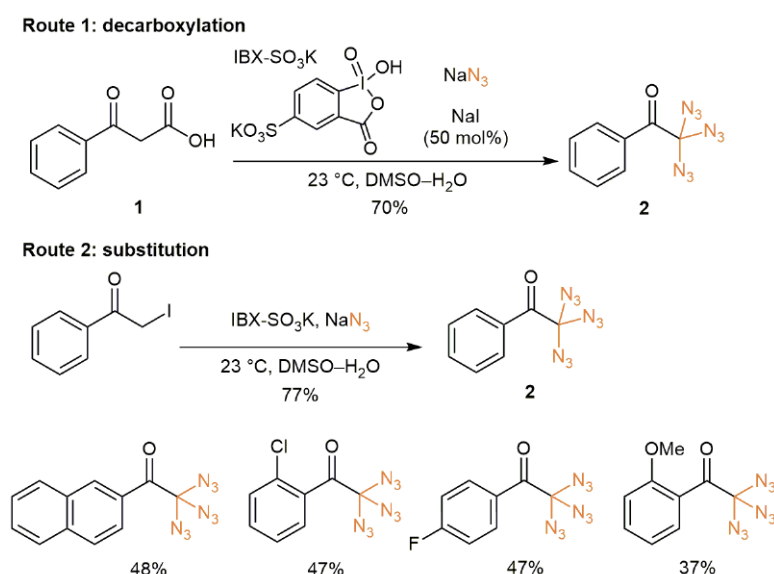
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■ The use of organic azides is ubiquitous in the functionalization of biomolecules through click chemistry, and also has many applications in materials science. These aspects led Professor Stefan Kirsch and his research group at the Bergische Universität Wuppertal (Germany) to develop an interest in the direct installation of the azide moiety through the oxidative functionalization of enolizable compounds with a simple azide source, preferably sodium azide. Professor Kirsch explained: “When we began our studies, the major goal was to achieve the azidation reaction in a highly chemoselective manner. To this end, a sulfonylated derivative of 2-iodoxybenzoic acid, IBX-SO<sub>3</sub>K, was developed that, in combination with sodium iodide, showed a perfectly balanced oxidation power to convert 1,3-dicarbonyls into their mono- and diazides in the presence of numerous functional groups. This method allowed the exchange of all hydrogens for azides at the easily enolizable position.”

Upon publication of their results (see: *Chem. Eur. J.* **2012**, *18*, 1187), they wondered whether the same azidation strategy could lead to azidated carbonyl compounds through a concomitant decarboxylation when malonic acid monoesters

were employed. Indeed, Dr. Philipp Klahn was able to show that the reaction of malonic acid monoesters with NaN<sub>3</sub> in the presence of IBX-SO<sub>3</sub>K and substoichiometric amounts of NaI in aqueous DMSO led directly to the formation of  $\alpha$ -azidoesters, a class of compounds that might be of future interest as potential precursors of  $\alpha$ -amino acids. Next they turned their attention to the decarboxylative azidation of the very similar 3-oxocarboxylic acids (such as **1**), where Professor Kirsch expected to find the azidoacetophenone **3** as the azidated product, or even higher azidated derivatives thereof. Professor Kirsch recalled: “However, the mono-azidated compound was not formed, and instead Philipp isolated, after work-up, column chromatography and concentration with the rotary evaporator, the novel azide-containing compound **2**. I was quite puzzled when the <sup>1</sup>H NMR spectrum of **2** did not show a single hydrogen at the  $\alpha$ -position, thus revealing a quaternary carbon.”

Much analytical work was required to accurately determine the structure of the geminal triazide **2**, since determination of the accurate mass of the molecule ion failed, and less azidated species were also possible. Professor Kirsch

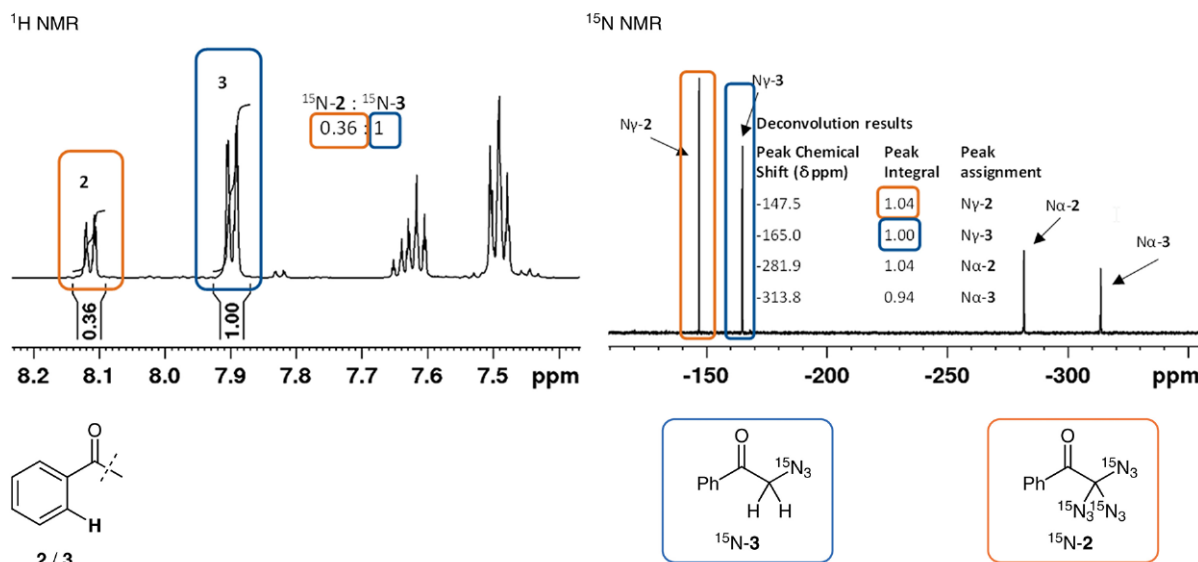


remarked: “Moreover, we were quite reluctant in the beginning to accept the structure of the geminal triazide, because we did not expect that these nitrogen-rich compounds were stable enough to be isolated with the standard experimental repertoire of synthetic chemists.” He continued: “Our first analytical proof for the triazide structure was from the reaction with cyclooctyne that gave the corresponding tris-1,2,3-triazole derivative through triple click reaction.” Two other members of the group, Dr. Andreas Kotthaus and Hellmuth Erhardt, then planned an exciting NMR experiment to directly determine the degree of azidation of **2** by studying a mixture of  $^{15}\text{N}$ -labelled **2** and **3**. Professor Kirsch said: “They obtained the  $^1\text{H}$  and  $^{15}\text{N}$  NMR data and were able to calculate from the integrals in both spectra that **2** has a nitrogen content three times as high as that of the known monoazide **3**: it was clear that the new compound **2** we had synthesized and isolated was the geminal triazide.”

When Dr. Klahn was able to develop a more straightforward route toward this new class of compounds that did not rely on a decarboxylation step, a simple access to a broad range of previously unknown triazides was found. Several  $\alpha$ -iodomethyl aryl ketones were successfully poly-azidated in the presence of IBX- $\text{SO}_3\text{K}$  and  $\text{NaN}_3$  in aqueous DMSO.

Professor Kirsch concluded: “Geminal triazides are not substances that everybody would work with, and one should always take appropriate caution before handling them. However, this is a new class of compounds that might have useful properties, for example as energetic plasticizers. The unusual structure of the triazide functionality holds great potential for discovering even more interesting chemistry.”

Matteo Zanda



### About the authors



*Prof. S. F. Kirsch*

Stefan F. Kirsch received his undergraduate education at Philipps-Universität Marburg (Germany) and obtained the Diploma degree in 2000. After his PhD thesis at Technische Universität München (Garching, Germany) with Professor Thorsten Bach (2000–2003), he moved as a postdoctoral fellow to the University of California at Irvine (USA) to work with Professor Larry E. Overman. In 2005, he returned to Technische Universität München. In 2011, he accepted an offer as Full Professor in Organic Chemistry at Bergische Universität Wuppertal (Germany). His work focuses on the development of new transition-metal-catalyzed domino reactions, oxidative functionalizations, and their applications in total synthesis.



*Dr. P. Klahn*

Philipp Klahn worked from 2002–2005 as laboratory technician at Altana Pharma (Germany). He received his undergraduate education at Technische Universität München and obtained his MSc in 2010. Afterwards he completed his PhD in the research group of Professor Stefan F. Kirsch in München and Wuppertal, dealing with, among others, the development of novel azidation protocols for carbonyl compounds. He is currently a Feodor-Lynen postdoctoral fellow at Rice University (USA) where he is working with Professor K. C. Nicolaou on the total synthesis of complex natural products.



*H. Erhardt*

Hellmuth Erhardt completed his undergraduate studies at the Nuremberg Institute of Technology (Germany) and obtained his MSc in 2013. He then joined the research group of Professor Stefan F. Kirsch at the Bergische Universität Wuppertal where he is currently continuing with his PhD studies in the field of polyazides.



*Dr. A. F. Kotthaus*

Andreas F. Kotthaus received his PhD in 2005 under the guidance of Professor Hans-Joseph Altenbach at the Bergische Universität Wuppertal. He then moved to the biochemicals company BACHEM (Switzerland) where he worked as a team leader in the production of peptides. In 2008 he returned to Wuppertal as a permanent research associate in the group of Professor Stefan F. Kirsch.