N-Monoacylation of Sulfonimidamides

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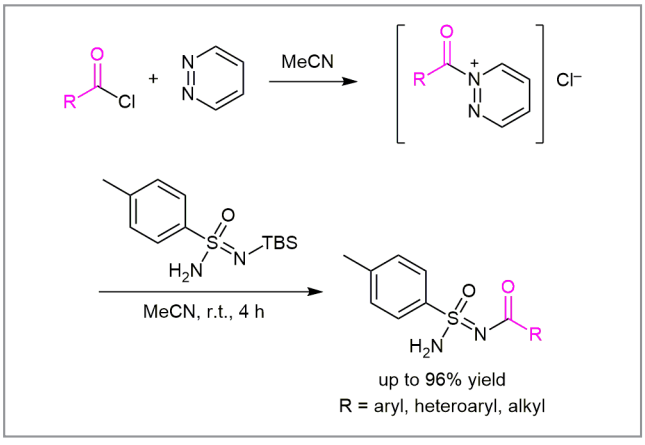
In recent years, *N*-alkylation, *N*-acylation and *N*-arylation of sulfonamides have proven useful in organic chemistry and medicinal chemistry for producing bioactive compounds and drug candidates. Sulfonimidamides (SIAs), the aza analogues to sulfonamides, have been introduced as an interesting but underexplored area of chemistry. Functionalization of SIAs has been conducted in medicinal chemistry programs; however, an interesting challenge for functionalization of an unprotected primary SIA is that both the sulfonamidic nitrogen and the imidic nitrogen can be functionalized. Recently, Dr. Yantao Chen of AstraZeneca Innovative Medicines Cardiovascular and Metabolic Diseases (Mölndal, Sweden) published in *Synthesis* a convenient synthetic method to produce monoacylated SIA products from TBS-protected starting materials, using a stoichiometric acylating reagent which was prepared by mixing an acyl chloride with one equivalent of pyridazine. Dr. Chen explained: "Under the reaction conditions, monoacylated products were obtained. Moreover, the TBS protecting group was removed during the reaction course. The paper also demonstrated one example of further functionalization on the second nitrogen starting from a mono-acylated product."



Scheme 1

"Following our first publication (*RSC Advances* **2015**, *5*, 4171), TBS-protected SIAs can be prepared on a large scale as starting materials for further chemical exploration," said Dr. Chen. This paper demonstrates an easy chemical process for the synthesis of *N*-acylated SIAs. "Through tautomerization, the achieved product is converted into the *N*(imidic)-acylated product, in which the amidic nitrogen is still free for another functionalization," continued Dr. Chen. He concluded: "Looking forward, we believe that this step-by-step functionalization provides us a method for performing more versatile functionalizations of the target substrates. For instance, when the first nitrogen in an SIA is acylated (i.e., protected), then the other one is free for other functionalization, such as acylation, alkylation, arylation, etc."

About the author

Dr. Y. Chen

Yantao Chen was born in LaiZhou, ShanDong (P. R. of China), in 1969. He received his B.S. in chemistry from ShanDong Normal University (P. R. of China) in 1991. Then he moved to Beijing and started his journey as an organic synthesis chemist. Under the supervision of Professor Wenting Hua, he explored and patented a novel synthetic approach of Ramipril – an angiotensin-converting enzyme (ACE) inhibitor, and obtained his M.S. from Peking University (P. R. of China) in 1994. During 1994–1997, he focused on the synthesis of chiral macrocycles and received his Ph.D. in 1997 under the supervision of Professor Wenting Hua. Then he spent two years at the Institute of Chemistry, Chinese Academy of Sciences (Beijing), as a postdoctoral scholar under Professor Duanfu Xu. In 1999, he moved to Linköping University (Sweden) for his postdoctoral research in the area of antimalaria under the supervision of Dr. Åsa Rosenqvist, Professor Ingemar Kvarnström and Professor Bertil Samuelsson. In July 2001, he was employed as a senior research scientist at Thin Film Electronics AB (Sweden), where he was trained to work in a clean-room lab. His work focused on the design and safety evaluation of polymerization reactors, polymer characterization by NMR and DSC, and surface modification chemistry. In 2003, he joined AstraZeneca R&D Mölndal (Sweden), and started his career as a senior research scientist. Over the last 13 years, he has been working in the Medicinal Chemistry Department at the Innovative Medicines of Cardiovascular and Metabolic Diseases (CVMD iMed), and contributed to both lead generation and lead optimization projects. Over the years he has supported numerous projects by designing new ideas for SAR study, exploring new synthetic routes, and being a project coordinator with outsourcing partners. As a member of the Compound Collection Enhancement (CCE) panel, he has designed several libraries for lead identification and lead optimization projects. He was rewarded for his contributions of bringing the awareness of 'Synthetic Reagent Initiatives' (AZ SRI) to the department, leading, managing, supporting SRI in the department, and communicating with SRI members and CRO partners. It is noteworthy that AstraZeneca offers chemists great computational tools and platforms that enabled him to become a competitive and skilled organic and medicinal chemist. Recently, he has focused on the chemistry of sulfonamides, sulfonimidamides, and sulfoximines, etc., trying to provide this underexplored chemistry more room in drug discovery. So far, he has designed and published two papers about sulfonimidamides.