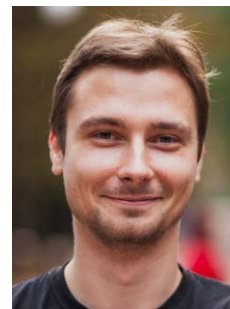


SYNLETT Spotlight

Imidazole-1-sulfonyl Azide Hydrochloride

Compiled by Maksim Fomich



This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Maksim Fomich was born in 1989 in Zhodzina, Belarus. He obtained his Specialist degree from Belarusian State University (2012) and then moved to the National Academy of Sciences of Belarus where he received his M.Sc. in chemistry (2013). Currently, he is working towards his Ph.D. under the supervision of Dr. Vadim V. Shmanai at the same institution. His research focuses on click chemistry for bioconjugation as well as on the synthesis of isotope-reinforced biomolecules and their derivatives.

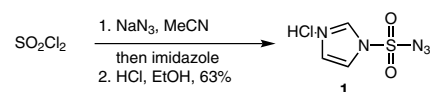
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Introduction

Imidazole-1-sulfonyl azide hydrochloride (**1**) is a white, slightly hygroscopic solid (mp 100–102 °C) that is soluble in water, acetonitrile, DMSO, DMF, and lower alcohols. It was reported by Goddard-Borger and Stick as a crystalline, shelf-stable, and easily prepared alternative to triflyl azide (TfN₃) in diazotransfer reactions.¹ It is widely used to prepare organic azides from aminosugars, aminoacids, and anilines because of its solubility in water. In addition, this reagent allows conversion of substrates with activated methylene groups into diazo compounds.^{1,2}

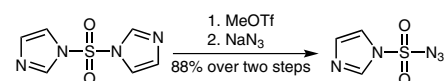
The preparation of imidazole-1-sulfonyl azide is conducted by a convenient two-step procedure (Scheme 1).¹ First, sulfonyl chloride is reacted with NaN₃ to give ClSO₂N₃,

which then reacts with imidazole. The crude base product is precipitated by ethanolic HCl.



Scheme 1 Goddard-Borger's synthesis

To minimize explosion risks, a safer synthesis starting from sulfonyl diimidazole was developed (Scheme 2).³

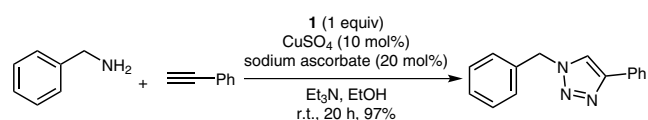


Scheme 2 Wang's synthesis

Abstracts

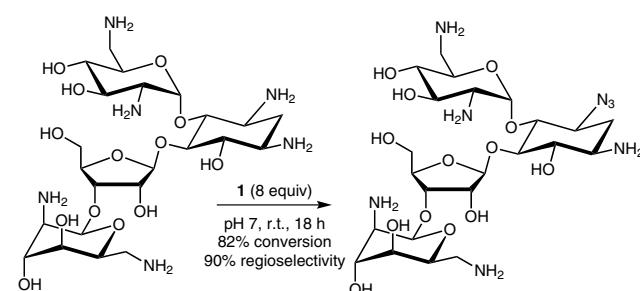
(A) One-Pot Click Synthesis of Triazoles:

Smith et al. utilized imidazole-1-sulfonyl azide hydrochloride to establish a one-pot procedure for the synthesis of 1,2,3-triazoles from primary amines and terminal acetylenes.⁴ The diazotransfer and click reactions were catalyzed by copper, and triethylamine was used as a base.



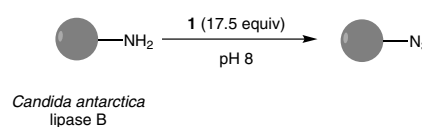
(B) Regioselective Conversion of Primary Amines into Azides:

Bastian et al. succeeded in the site-selective diazotransfer to neomycin B. The six amino groups of the substrate differ slightly in pK_a (from 5.7 to 8.8). Control of pH and high excess of imidazole-1-sulfonyl azide hydrochloride allowed the insertion of azide into the position of the least basic amine.⁵



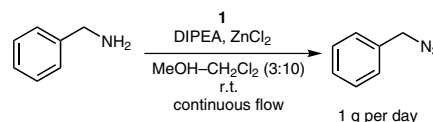
(C) Introduction of Azide Groups into Proteins and Peptides:

Azide **1** was found to be an appropriate diazo-donor reagent for the introduction of azides in place of the amines of lysine residues or N-termini in aqueous media.⁶ Later the reaction was shown to proceed without adding copper(II) and at a pH as low as 8.5. In addition, selective diazotransfer to N-termini and α -amines at this pH was observed,⁷ and the use of **1** in solid-phase peptide synthesis was demonstrated.⁸



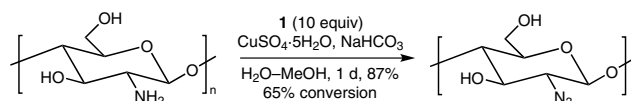
(D) Synthesis of Organic Azides in a Continuous Flow System:

The reaction between benzylamine and **1** was used for the optimization of a continuous flow system for the preparation of organic azides. Temperature, residence time, and stoichiometric ratios were optimized.⁹



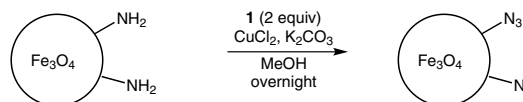
(E) Preparation of Azide Polymers and Dendrimers:

Preparation of azide-modified polymers for further click chemistry reactions was achieved with **1**. This approach showed better results for chitosan as compared to TfN₃, azidated epichlorohydrin, and a diazotization–substitution approach.¹⁰ Also, it was used for successful synthesis of fully and partially azido-derivatized PAMAM G4 dendrimers,¹¹ peptide-polymer nanotapes,¹² polymeric bifunctional ligands,¹³ and solid supports.¹⁴



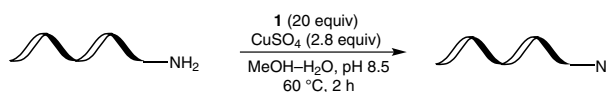
(F) Preparation of Azide Nanoparticles:

McCarthy et al. described an amine–azide conversion on magnetic nanoparticles. Interestingly, only two equivalents of **1** and a submilligram quantity of copper(II) chloride are recommended. FTIR was used to control the diazotransfer.¹⁵



(G) Introduction of Azide Groups into Oligonucleotides:

1 allowed the clean and efficient introduction of azide groups into the 5'-, 3'-, and internal positions of oligonucleotides. Unfortunately, oligoribonucleotides and solid-supported oligonucleotides were found to be unstable under the reaction conditions.¹⁶



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