Abstract

Azides are organic or inorganic compounds characterized by their diverse reactivity and "energy richness". A special feature of azides is their extraordinary reactivity due to their 1,3-dipolar structure.

Over the years, more and more reactions of azides have been explored, including the CURTIUS rearrangement, the STAUDINGER reaction, and the HUISGEN reaction. Special mention deserves the latter since the copper-catalyzed variant (CuAAC) became an important component of click reactions. Further modifications, such as the strain-promoted azide-alkyne cycloaddition, increased biorthogonality due to avoiding cell-toxic copper(I) salts.

In addition to their application in organic reactions, the photochemistry and the thermal decomposition of azides are also exploited. The resulting reactive nitrenes enable a linkage between different molecules and the formation of aziridines. Furthermore, the thermal decomposition of polyazides leads to porous frameworks called ATFs. This makes them an important building block in material science.

In this work, various polyazides were developed using different synthesis routes. Based on the copper-catalyzed reaction of boronic acids and boronic esters with sodium azide, several small diazides based on benzene derivatives were prepared. The synthesized organic azides could be handled safely despite the high nitrogen content. Based on previous work, Hyper Crosslinked Polymers were synthesized and analyzed by IR-spectroscopy, elemental analysis, and nitrogen adsorption to investigate the difference between unsubstituted and substituted diazidobenzenes.

More complex compounds that can function as crosslinkers were synthesized primarily using three aromatic azide-containing building blocks. In addition, ether synthesis with highly fluorinated benzyl bromide has been established. Additionally, based on literature, known crosslinkers, 4-azido-2,3,5,6-tetrafluorobenzoic acid, was used in ester synthesis.

Furthermore, C_3-symmetric structures based on trimethyl 2,4,6-triaminobenzene-1,3,5-tricarboxylate were prepared, which gave insight into the reactivity of this complex building block. In addition to azide synthesis, this building block

has also been tested in alkylation, Ullmann coupling, and Sandmeyer-like reactions.

1 Introduction

1.1 Azides

Organic azides are an important and useful class of reagents, Phenyl azide as their first representative was synthesized by Peter Grieß in 1864. At the end of the 19th century, the scientific community intensively discussed the molecular structure of azides. Curtius and Hantzsch postulated a cyclic structure, 20 years later, Thiele suggested the linear structure, which was confirmed later (Figure 1).[1-3]

$$R-N=N\equiv N \qquad R-N\overset{N}{\underset{N}{\langle\,\|}}$$

Figure 1: Postulated structures of azides. The linear structure was suggested by Thiele (left), and the cyclic structure was proposed by Curtius and Hantzsch (right).

Since the first report of azides, many reactions like the Curtius rearrangement or the Staudinger reaction have been developed. In the 1950 and 1960, investigations in the application of azides lead to a growing importance for the industrial synthesis of heterocycles[4]. In 2001, azides experienced another upswing due to the development of the concept of click-chemistry by K. B. Sharpless.[5] The work of K. B. Sharpless, C. Bertozzi, and M. Meldal in the field of click reactions and biorthogonal chemistry was awarded with the Nobel prize in 2022.[6]

Azides can be classified as potential explosives based on their ability to decompose into molecular nitrogen and a highly reactive nitrene. Ionic azides like sodium azide are relatively stable and often used in azide synthesis, while heavy metal and covalently bound azides are thermally decomposable and often explosive. Many literature-known organic azides can be classified as non-explosive and therefore safe to handle, like tetrakis(4-azidophenyl)methane (**1**) (Figure 2),[7] however, several extremely explosive compounds have also been reported.[4-5] Tetraazidomethane (**2**) and 1-diazidocarbamoyl-5-azidotetrazole (**3**) (also called azidoazide azide) are two examples for organic azides with enormous nitrogen content, which are extremely explosive (Figure 2). Pure compounds **2** and **3** can decompose spontaneously without any impact.[8-9]
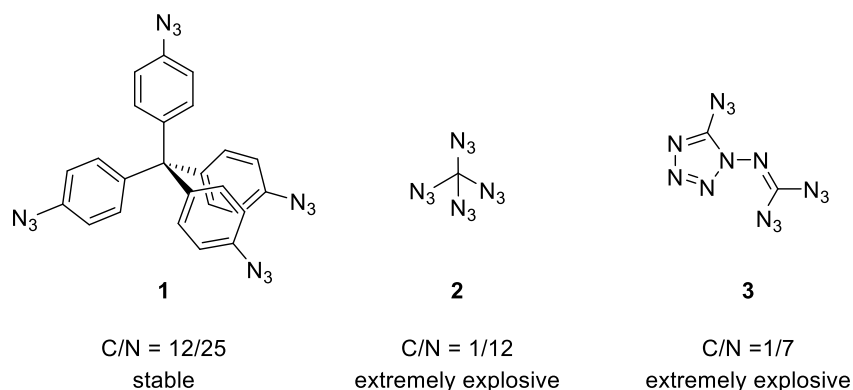
Figure 2: Examples for stable and explosive azides and their carbon-to-nitrogen ratio.[7-9]

There are two rules reported in literature that shall help to estimate the stability of organic azides:

1) carbon/oxygen to nitrogen ratio by SMITH *et al.*[10-11]:

$$\frac{(N_C + N_O)}{N_N} \geq X\,, (N = Number\ of\ atoms).$$

The rule considers the ration of carbon and oxygen to nitrogen and therefore allows a classification of their tendency to decompose violently. Molecules with a ratio greater than three can be considered non-explosive and handled safely, while molecules with a value between one and three are highly unstable and should be synthesized and handled with care. Compounds with values lower than one can be extremely dangerous and should never be isolated.[4]

2) rule of six

To render a compound relatively safe, a molecule should contain at least six carbon atoms (or other atoms of about the same size) per energetic group.[12]

In addition to their property of being able to decompose violently, in particular the explosiveness of heavy metal salts, the toxicity of inorganic azides should also be mentioned. With an LD_{50} in rats of 27 mg/kg, the toxicity of sodium azide is comparable with the one of cyanides.[13]

Even though the azide structure is often drawn linear with angles of 180° for N^1-N^2-N^3 and 120° for C-N^1-N^2, the angles of the bonds differ slightly. In 1996, NGUYEN and SENGUPTA calculated the angles of methyl azide (Figure 3), which were found to be 172.5° (N^1-N^2-N^3) and 115.2° (C-N^1-N^2). The N^1-N^2 bond (1.244 Å) was slightly longer than the N^2-N^3 bond, which was determined to be 1.162 Å.[14] In the same year, FANG *et al.* calculated the bond angles of phenyl

azide in S_0, S_1, and T_1 states. In the S_0 state, the angles were found to be 168.6° for N^1-N^2-N^3 and 122.1° for C-N^1-N^2. According to the calculated bond length of methyl azide, the N^1-N^2 bond was longer than the N^2-N^3 bond with 1.259 Å and 1.134 Å.[15]
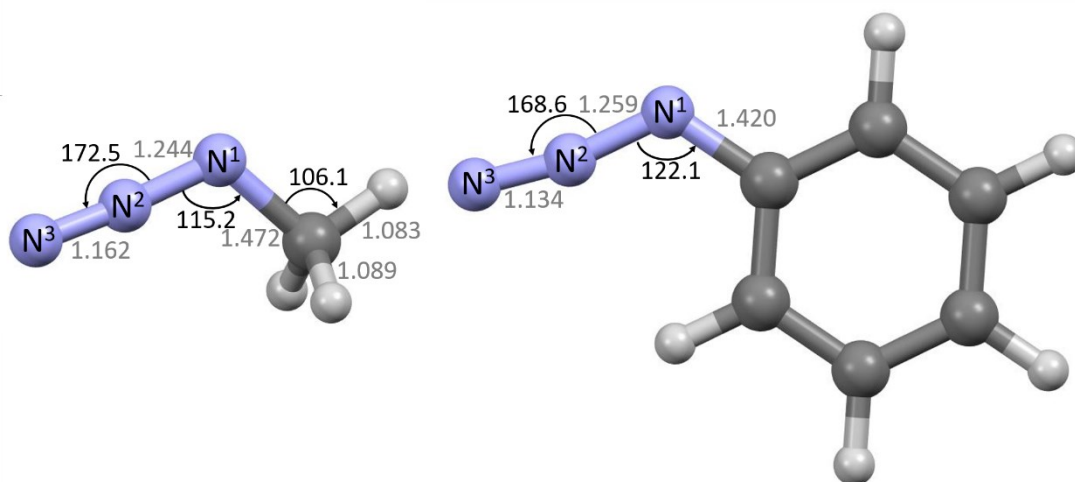

Figure 3: Bond angle and length of methyl azide (left)[14] and phenyl azide (right)[15]. Bond lengths are given in Ångströms, and bond angles in degrees.

1.1.1 Synthesis

Many ways to synthesize azides have been reported over the past years. Since the synthesis of alkyl and aryl azides differs, several synthesis methods are presented in this chapter.

Alkyl azides are commonly synthesized by nucleophilic substitution using sodium azide. ZHANG *et al.* reported the use of a chiral cationic pentanidium catalyst to enable the enantioconvergent nucleophilic substitution of activated tertiary bromides to obtain different compounds with yields ranging from 67% to 86% and enantiomeric excesses (*ee*) up to 97%.[16] Besides this, alkyl azides are accessible by the *MITSUNOBU* reaction,[17-18] C-H activation[19], or 1,2-addition reactions.[4, 20]

In case of aryl azides, several synthetic routes are used, including the synthesis of aromatic azides from diazonium salts, organometallic reagents by nucleophilic aromatic substitution, and copper-mediated conversion of boronic esters and acids.

Diazotization allows to the synthesis of azides out of aromatic amines. The reaction mechanism between the diazonium salt and the azide is still in discussion. Hereby, three mechanisms are discussed as plausible. The first one is

similar to the solvolysis mechanism of diazonium salts consisting of a S_N2Ar. Previous reports using computational studies and experiments with radio-labeled compounds showed that this reaction mechanism is not observed. Another possibility is the formation of a 1H-pentazole cycloadduct by thermal [3+2] cycloaddition followed by a retro [3+2] reaction to yield the azide. The third plausible mechanism describes an addition-elimination process *via* an acyclic intermediate. While the first prediction was shown not to occur, the second and especially the third mechanism are plausible (Scheme 1).[21]
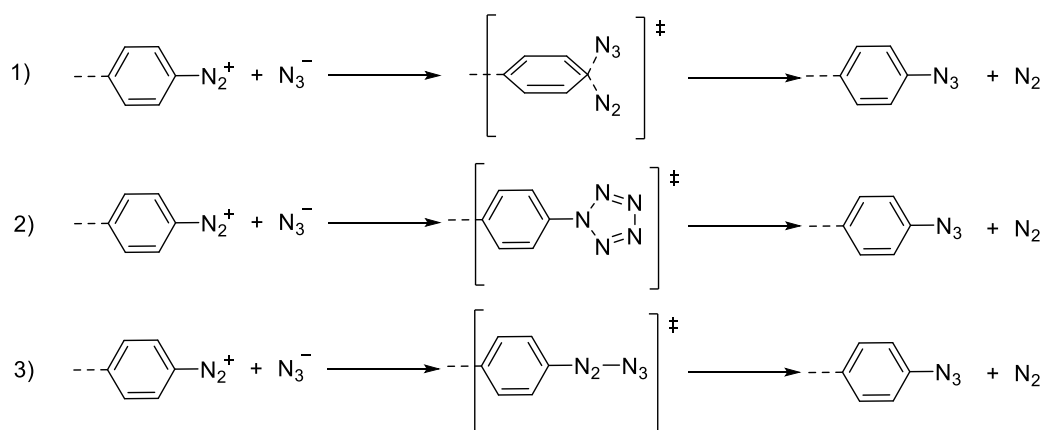

Scheme 1: Discussed mechanisms for the azide formation, starting with diazonium salts. According to computational studies and experiments with radiolabeled nitrogen, the first mechanism seems implausible, whereas the second and especially the third seem very likely.

For synthesizing azides starting from organometallic compounds, many methods have been developed over the years, such as the reaction of GRIGNARD or lithium reagents with tosyl azide (Scheme 2).[5, 22-23]

Additionally, aryl azides can readily be synthesized in good yields by nucleophilic aromatic substitution reactions (S_NAr). Therefore, electron-poor aromatic systems with electron-withdrawing groups attached, like pentafluorobenzylaldehyde, are reacted with sodium azide.[4-5, 24-25]

Based on the approaches on copper-catalyzed coupling reactions by LAM *et al.*,[26] several groups developed and optimized the copper-catalyzed synthesis of azides.[27-28] This method enables the synthesis of azides in excellent yields. Another advantage are the mild reaction conditions applied and a wide range of functional groups, which is tolerated.[28-29]
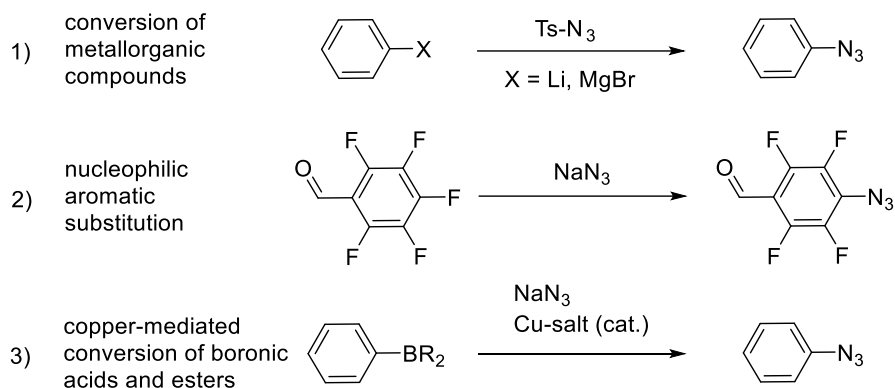
Scheme 2: Different synthesis pathways for the formation of aromatic azides. 1) conversion of metalorganic compounds, e.g., GRIGNARD or lithiated compounds; 2) nucleophilic aromatic substitution, e.g., pentafluorobenzaldehyde; and 3) copper-mediated conversion of boronic acids.

1.1.2 Reactions

Due to their electronic properties, azides are able to react with electron-deficient compounds (electrophiles) at nitrogen position 1 and with nucleophiles at position 3. This can be illustrated by their mesomeric structures shown in Scheme 3. The combination of a nucleophilic attack on N^3 and the addition of N^1 to an electrophile results in a cycloaddition. Since azides are 1,3-dipoles, the cycloaddition can be specified as 1,3-dipolar cycloaddition. Another possible process is the formation of a nitrene by the extrusion of molecular nitrogen, which will be explained in more detail in the following chapter.[4]
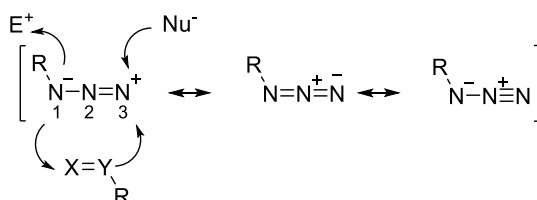
Scheme 3: Mesomeric structures and reactivity of azides.

In comparison to other 1,3-dipoles, azides are remarkably stable, and dimerization and/or hydrolysis are not observed.[4]

The most popular reactions of azides include, e.g., the STAUDINGER reaction, the CURTIUS rearrangement, and cycloaddition reactions like the copper(I) catalyzed azide-alkyne cycloaddition (CuAAC).

The STAUDINGER reaction describes the reduction of an azide to a corresponding amine using a phosphine (Figure 4). Isocyanides and their secondary products are accessible *via* the CURTIUS rearrangement. In this process, acyl azides are

decomposed by irradiation or thermal decomposition and undergo a rearrangement leading to the isocyanides. Different products like carbamates or amines can be obtained depending on the workup conditions.[30]

$$R-N_3 \xrightarrow[\text{2) } H_2O]{\text{1) } PR_3} R-NH_2$$
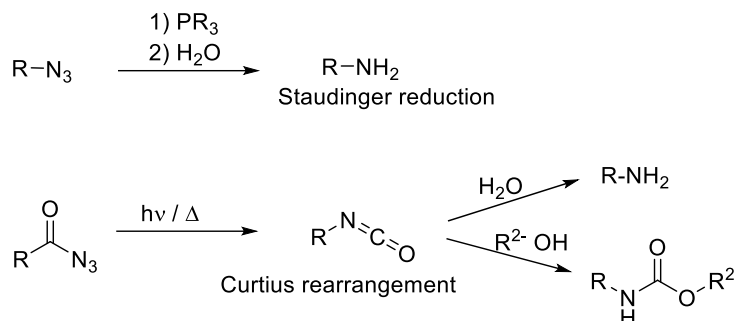Staudinger reduction

Figure 4: Exemplary reactions of organic azides. STAUDINGER reaction and CURTIUS rearrangement are shown.

Azides can easily undergo 1,3-dipolar cycloaddition with different types of dipolarophiles. This reaction is also called the HUISGEN reaction, named after R. HUISGEN, who elucidated the mechanism.[31] According to the WOODWARD-HOFFMANN rules, the reaction occurs in a (4n+2) thermally allowed, concerted cycloaddition (Scheme 4).[32] The breakthrough of this reaction occurred about 40 years later when SHARPLESS introduced the concept of Click Chemistry. The term Click Chemistry includes strict reaction criteria: The reaction has to be modular, wide in scope, and stereoselective. In addition, high yields must be achieved. Byproducts must be inoffensive, and their separation must be feasible with nonchromatographic methods. Simple reaction conditions, readily available starting materials, no benign or easily removable solvent, and simple product isolation (nonchromatographic methods) complete the process characteristics of Click-reactions.[12]

The HUISGEN reaction is not able to fulfill all these criteria. In 2002, the groups of MELDAL and SHARPLESS published the first CuAAC.[33-34] Compared to HUISGEN reactions, the CuAAC results only in 1,4-disubstituted 1,2,3-triazoles, while the non-copper catalyzed reaction generates the 1,5-disubstituted isomer. The exchange of the catalyst to ruthenium(II) allows the synthesis of 1,5-disubstituted 1,2,3-triazoles exclusively.[35-36]
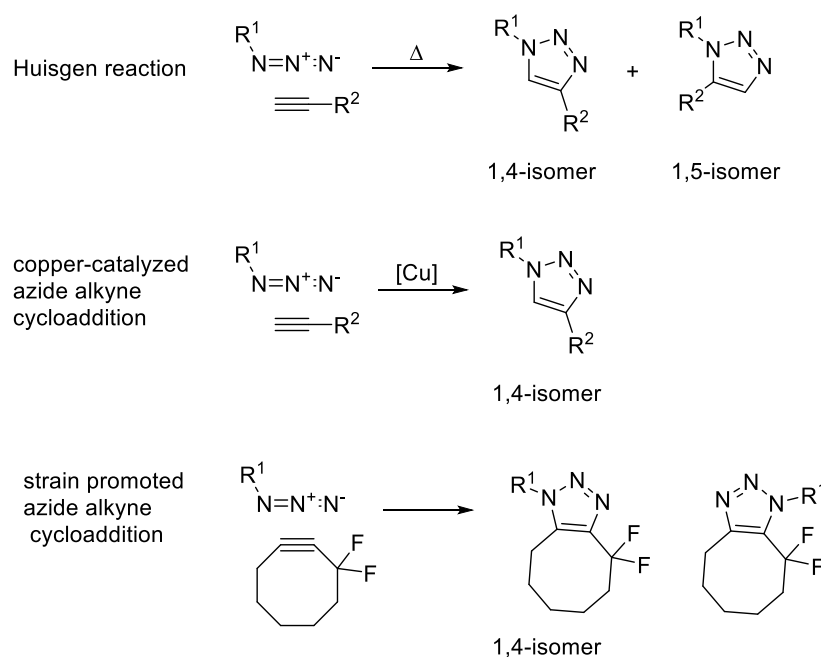
Scheme 4: Cycloaddition of an azide and an alkyne. The Huisgen reaction leads to both the 1,4- and 1,5-isomer. The 1,5-isomer can be suppressed using copper(I) salts as catalysts. The strain-promoted cycloaddition enables the synthesis of triazoles without using toxic copper salt.

Due to their diversity and simplicity, click reactions found their way in material science. Besides their intensively studied application in modifying polymers and surfaces, organic porous polymers based on click reactions were reported.[37-38]

Another success was achieved by the Bertozzi group, developing a copper-free version using strained alkynes. This reaction leads to both isomers, the 1,4- and 1,5-substituted products, but due to the renouncement of copper, this reaction is applicable in living systems. [39]

1.1.3 Nitrene chemistry

Nitrenes are highly reactive species, most commonly generated by the photolysis or thermolysis of organic azides. Moreover, they are accessible *via* isocyanates or α-elimination of, e.g., *N*-arylsulfonyloxy-carbamates. Reductive nitrene formation of nitro and nitroso compounds, as well as oxidative nitrene formation, are further possibilities. This is caused by the ability of nitrogen, when covalently bonded, to occur in the oxidation states +5 to -3 and to switch easily between these oxidation states.[40] The chemical structure of nitrene is related to the structure of the carbene, however, both have different

properties. In contrast to phenyl carbene, the gap between phenyl nitrene's singlet and triplet state is much larger, with a value of about 18 kcal/mol. In accordance with HUND's rule, nitrenes have triplet ground states. Electron spin resonance studies have obtained evidence for this at very low temperatures.[41] Modern time-resolved spectroscopic techniques and high-level *ab initio* calculations enabled a detailed analysis and description of aryl azide photochemistry. One of the most investigated organic nitrenes is phenyl nitrene, possible reaction pathways of phenyl nitrene can be depicted in Scheme 5. Different products can be formed depending on the applied conditions of the photo- or thermolysis, particularly the reaction temperature and solvent used. Triplet nitrene **9** formation is favored in low temperature rigid glasses, whereas in solution at ambient temperature and in inert gas matrices at around 10 K, the formation of ketenimine **7** is preferred. By EPR studies, it was found that the triplet state of phenylnitrene is the ground state.[42] However, this species is extremely light sensitive and rapidly isomerizes to the ketenimine above 77 K.[43]

Photolysis in the presence of primary or secondary amines leads to the formation of azepines *via* azirine **6** and/or ketenimine **7**. Polymeric tars formed during thermolysis, or photolysis, can be suppressed by high dilution of the solution, resulting in the formation of azobenzene **12**.[44-46]