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Synthesis of Diaziridines and Diazirines via Resin-Bound Sulfonyl Oximes

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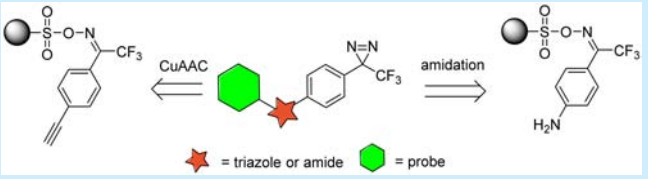
Supporting Information

ABSTRACT: Diazirines are one of the most prominent functionalities in labeling experiments in vivo and in vitro because they allow photochemical generation of carbenes. The strategy presented herein describes the formation of diaziridines, being essential precursors in diazirine syntheses, using solid-supported procedures with immobilized sulfonyl oximes. The solid-supported building blocks have been shown to be valuable intermediates for CuAAC and amidation reactions, offering the possibility to build complex compounds with diverse functionalities.



Diazirines play a pivotal role in modern synthetic chemistry and biochemistry because they are well-known precursors for the syntheses of carbenes. They form, besides the compound classes of benzophenones and azides, the most important group of photoactive reagents being used for labeling experiments.[1] The diazirines gained particular importance due to their small size and the advantageous excitation wavelengths of the three-membered ring in biological experiments (ca. 360 nm).[2] Therefore, in comparison with other photoactivatable groups, diazirines offer ideal conditions for use in vivo and in vitro due to a slight steric influence in combination with minimum damage to the biological system (Figure 1).[3]

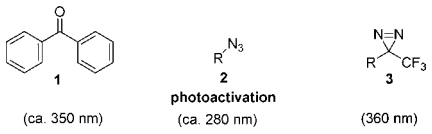
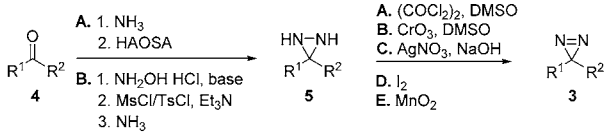


Figure 1. Three examples of functional groups that can be photochemically activated: benzophenones (**1**), azides (**2**), and diazirines (**3**).

Advantageous properties of labeling strategies with diazirines have been proven in many biological applications. Synthesis of the diazirine functionality and its chemical surrounding differs slightly depending on the biological target. Aliphatic diazirines[4] and aromatic derivatives[5] were used, and new substituents on the diazirine core continuously offer new applications in the field of biology.[6]

The most important strategy for the generation of diazirines **3** via the oxidation of diaziridines **5** was developed in 1963[7] and has since been an important reaction in the repertoire of organic chemists. Besides some procedures demonstrating the synthesis of diazirines from amidines,[8] diazirines are usually synthesized via a multistep procedure including the conversion of ketones into precursors, which allow the synthesis of diaziridines **5** and their oxidation to diazirines **3** (Scheme 1).

Scheme 1. Strategies for the Synthesis of Diaziridines 5 and Diazirines 3



HAOSA: hydroxylamine-O-sulfonic acid, MsCl: mesyl chloride; TsCl: tosyl chloride.

In a typical reaction sequence, ketones are converted into sulfonyl ketoximes via an oxime formation and successive tosylation or mesylation.[9−11] Those tosyl and mesyl ketoximes can be reacted in liquid ammonia to the corresponding diaziridines **5** and are efficiently transformed in an additional step to give diazirines **3**. The key step of a diaziridine synthesis, the ammonia-mediated formation of the three-membered ring, requires equipment efforts because ammonia has to be condensed at low temperature (−78 °C).[12] Other alternatives are known that describe the diaziridine formation via the use of ammonia dissolved in solvents such as dioxane or methanol.[13] Concerning the oxidation of diaziridine precursor **5** to the target diazirine **3**, one can choose among diverse well-established procedures (Scheme 1).[14] Formation of diazirines and their reactions (e.g., attachment of biologically interesting compounds for in vivo or in vitro investigations) are widely used;[15] however, to the best of our knowledge, methods allowing the generation of this compound class on solid supports have not yet been

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developed. We investigated the potential of sulfonyl oxime linkers for the generation of diaziridines, via a solid-supported procedure, to provide an easily adaptable methodology for the synthesis of structurally diverse molecules with diazirine labeling. Development on solid supports aimed for the preparation of flexible strategies for the attachment of diverse building blocks as a basis for the combinatorial access to new diazirine−drug conjugates.

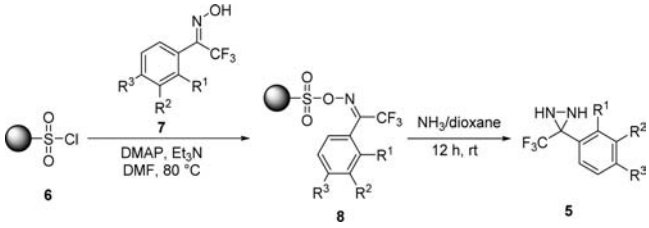
To develop solid-supported diazirine-forming procedures, relying usually upon tosyl oxime or mesyl oxime preparation, we envisaged the use of polystyrene−sulfonyl chloride as a polymer equivalent to commonly used mesyl or tosyl chloride. Comparable to the known reactions in solution phase (compounds **4** and **5**) (Scheme 1), we converted ketones into the corresponding ketoximes (**7**), via reaction with hydroxyl amine in a first step. We show that the resulting oximes can be immobilized via reaction with commercially available sulfonyl chloride linker **6** to give the desired solid-supported sulfonyl oximes **8** in one step. Several attempts to develop a procedure for the direct attachment of ketones, without the preparation of precursors in solution, have been investigated, but the attachment of presynthesized building blocks have been shown to be superior to the direct immobilization of ketones onto sulfonyl hydroxylamine linkers. While several different ketones have been used in the past for similar conversions, α,α,α-trifluoroacetophenones were selected as a model system for the establishment of this methodology on solid phases because the resulting diazirines with a 3-trifluoromethyl-3-phenyldiazirine core were investigated with respect to their use as photoactivatable reagents and their biological applications.[16] The presence of the trifluoromethyl group is particularly advantageous for the procedure presented herein as it facilitates the cleavage of the immobilized precursors from the solid supports and therefore allows good results for diazirine formation. In addition, the CF_3 group is known to prevent the generation of byproducts during photolysis.[13,17]

The functional cleavage with ammonia/dioxane solution[13] was used in a second step to obtain a set of substituted diaziridines **5** (Table 1). Due to the use of a saturated solution of ammonia in an organic solvent, instead of liquid ammonia via condensation, the experimental effort has been minimized. This procedure allows, in combination with the use of a solid support as starting material, the application of this protocol to the synthesis of functionalized molecules in a combinatorial manner by parallel reactions. We have also been able to show that the described procedure is suitable for the transformation of aromatic trifluoroacetophenones with diverse substitution patterns and functional groups, furnishing diaziridines in very good yields (compounds **5g** and **5j**) (Table 1).

Compatibility of the immobilization and cleavage protocols with several aromatic building blocks (**8a−d**, **8g−i**) and alkyne groups (**8e,f,j**) has been shown. Target compound **5f** (Table 1, entry 6) is of particular interest for the improvement and application of the developed method because the generated linker **8f** offers the possibility to immobilize additional building blocks via Cu-catalyzed azide alkyne cycloaddition (CuAAC) reactions.

Beyond the introduction of additional building blocks in CuAAC reactions, the preparation of a sulfonyl-oxime-bound functional group for the modification of building blocks via amide formation was intended (Scheme 2). Advantages of CuAAC reactions and amidations revealing these transformations to be highly suitable for the attachment of new building blocks are mild reaction conditions and easily accessible reagents. Since many

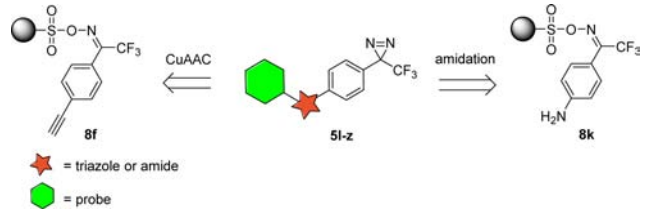
Table 1. Solid-Supported Synthesis of Sulfonyl Ketoximes and Their Cleavage for the Generation of Diaziridines 5



entry	8	R^1	R^2	R^3	5	yield, % (6 to 8/8 to 5)
1	8a	H	H	H	5a	72 (88/82)
2	8b	H	H	OMe	5b	80 (quant/80)
3	8c	H	H	Cl	5c	63 (quant/63)
4	8d	H	H	Br	5d	70 (quant/70)
5	8e	H	H	−CCTMS	5e	69 (quant/69)
6	8f	H	H	−CCH	5f	77 (quant/77)
7	8g		−(CH)$_4$−		5g	96 (quant/96)
8	8h	H	H	1′-OMe-phenyl	5h	63 (57/quant)[a]
9	8i	H	H	4-bromophenyl	5i	79 (98/81)
10	8j	H	H	4-ethinylphenyl	5j	97 (quant/97)

[a]Explanation for the discrepancy between the yield of single-step calculations and overall yields is given in the Supporting Information.

Scheme 2. Strategy for the Syntheses of Immobilized Alkyne and Amine Derivatives for the Syntheses of Complex Molecules with Diazirine-Labeled 5l−z



azides and carboxylic acids or their chlorides are readily available and commercial reagents can be gained easily, these reactions can be used for efficient strategies on solid supports. The necessary free amine functionality for an amidation strategy was gained by immobilizing previously synthesized 4-aminophenyl trifluoroethanone oxime (see Supporting Information) to solid support **8k** (Scheme 2). Both of the functionalized immobilized building blocks, the alkyne-functionalized resin **8f** and the amine derivative **8k**, were further modified on-bead in subsequent experiments. The investigations presented here describe the first CuAAC reactions and amidations involving sulfonyl oximes (while retaining the sulfonyl oxime functionality).

Since CuAAC reactions can be performed under mild conditions even on solid supports, they form a suitable method for the efficient attachment of further functional groups, linkers, or even small biologically active molecules. Out of many protocols for the CuAAC reaction in solution,[18] one of the most common procedures using CuI without any additional ligands was selected for the planned on-bead transformation. In a typical on-bead CuAAC reaction, using CuI in DMF with addition of water as solvent, diverse functionalized azides were successfully immobilized on solid supports (resin-bound alkyne **8f**) and then cleaved as triazole-derived diaziridines (Scheme 3). Building block 1-(4-ethynylphenyl)-2,2,2-trifluoromethylketox-

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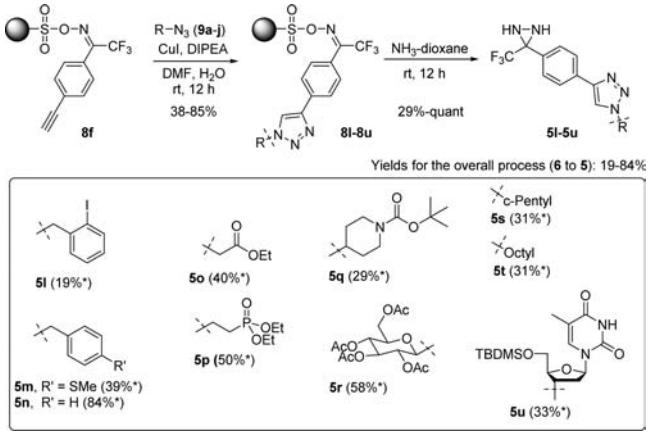
Scheme 3. Formation of 1,2,3-Triazole-Substituted Diaziridines via Modification of Resin-Bound Sulfonyl Oximes in CuAAC Reactions



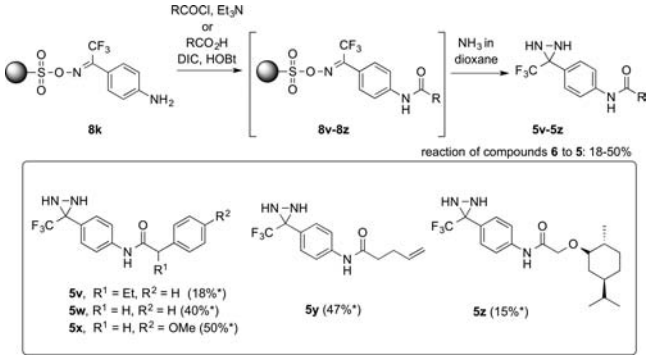
*Yields refer to the conversion of **8f** to **5l**–**5u** over two steps (see Supporting Information for details of the calculation of yields on solid supports).

ime, which was necessary for the synthesis of alkyne-modified sulfonyl oxime resin **8f**, was gained in a three-step synthetic sequence (for the synthesis of resin **8f**, see the Supporting Information). We demonstrated that azides without any functionalization (target compounds **5n**, **5s**, **5t**; Scheme 3), as well as functionalized derivatives with the option for further modifications (**5l**, **5o**–**q**, Scheme 3) can be attached successfully to the solid support. Additionally, synthesis of diaziridines **5r** and **5u** (Scheme 3) demonstrates the integration of naturally occurring building blocks (e.g., sugar units or nucleosides). As the immobilized sulfonyl oximes are prone to react with strongly nucleophilic reagents, building blocks bearing such functionalities have to be protected adequately prior to their use in this protocol.

Besides the on-bead modification via CuAAC reaction, we aimed for the development of amidations on solid support by conversion of immobilized amines with carboxylic acid derivatives. The building block necessary for the synthesis of amine-derived sulfonyl oxime resin **8k** was obtained in a synthetic sequence consisting of four steps (for synthesis of resin **8k**, see the Supporting Information). To avoid any influence of additional coupling reagents on the sulfonyl-based linker during the amidation, a conversion of the resin-bound amine with acid chlorides was chosen in initial experiments. Reactions of the linker **8k** with four different acid chlorides furnished the immobilized amides **8v**, **8w**, **8y**, and **8z**. In addition, conversion of **8k** as an example with a carboxylic acid and the peptide coupling reagents DIC/HOBT has been demonstrated successfully (**5x**) (Scheme 4). Subsequently, all of the resin-bound amides were cleaved from the solid phases by addition of ammonia dioxane solution, and the corresponding diaziridines **5v**–**5z** were obtained in moderate to good yields (Scheme 4).

A selection of the diaziridines that were synthesized during this work was oxidized to give the diazirines **3a**–**3j**. In the chosen protocol, which is used as a standard procedure for most of the diaziridine to diazirine conversions, oxidation is conducted with elemental iodine (3.3 equiv) in diethyl ether at room temperature. The reaction was shown to yield good to very good results for derivatives **3a**–**3f**, **3i**, and **3j** with reaction times of 12–18 h. The standard procedure had to be modified only for the oxidation

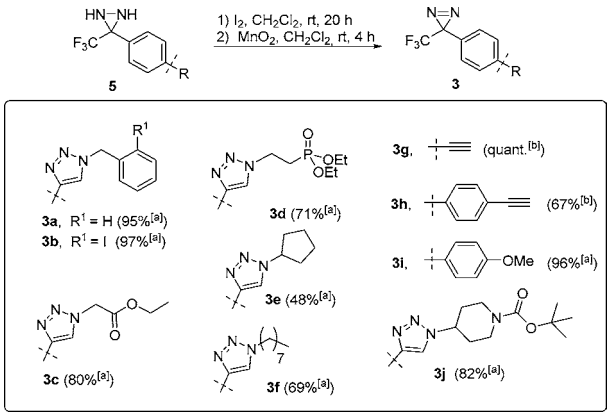
Scheme 4. Syntheses of Diaziridines 5v–5z via Functional Cleavage of Resin-Bound Amides



*Yield calculated over all steps on solid phases, starting with polymer supported sulfonyl chloride (**6**).

of diaziridines with an unprotected alkyne functionality (**5f**, **5j**) (Table 1), as the oxidation with iodine resulted in the occurrence of diverse byproducts (Scheme 5). Concerning the latter

Scheme 5. Oxidation of Diaziridines 5 Gained via Solid Phase Synthesis To Give Corresponding Diazirines 3



[a] refers to method 1), [b] refers to method 2).

diaziridines, the reaction with freshly prepared manganese dioxide was found to be suitable for a conversion to give the diazirines **3g** and **3h** in very good yields (Scheme 5).

Since the synthesis of the diazirines primarily aims for the investigation of receptor–ligand interactions via covalent binding of a carbene precursor to a biological target, the successful generation of the active carbene species is a prerequisite for the obtained diazirines. Successful activation of the diazirine functionality and its cleavage for the generation of carbenes was shown with two diaziridines, which were isolated after their formation on solid phases. For this purpose, the corresponding diazirines **3a** and **3f** were photochemically activated by exposure to irradiation in methanol-d_4. It was proven that the target compounds **10a** and **10b** can be obtained in very good yield and purity by irradiation with UV light at 360 nm, in accordance with known reactions of comparable systems,[19] which enables them for a use in labeling experiments (Scheme 6).

To the best of our knowledge, the present study describes for the first time the synthesis of diazirines via a solid-supported procedure. The given examples show that a synthetic sequence consisting of (1) attachment of ketoximes to the solid phases, (2) functionalization of the immobilized building blocks, (3)

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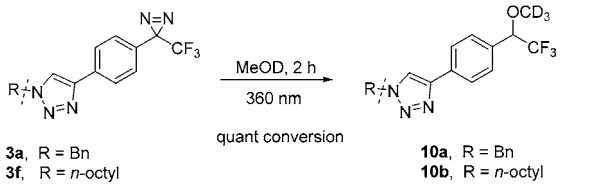
Scheme 6. Carbene Generation and Reaction in Methanol-d_4



3a, R = Bn
3f, R = *n*-octyl

10a, R = Bn
10b, R = *n*-octyl

functionalizing cleavage to give diaziridines, and (4) oxidation of the compounds is a valuable procedure for the synthesis of diazirines. The established protocols allow the flexible modification of solid-supported sulfonyl oximes for biological labeling experiments via combinatorial methods. To our knowledge, modifications of sulfonyl oximes via CuAAC and amidations with conservation of the sulfonyl oxime functionality are reported for the first time.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03252.

Experimental procedures and analysis of all target compounds and intermediates and copies of ^{1}H and ^{13}C spectra of the obtained diaziridines and diazirines (PDF)

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Notes

The authors declare no competing financial interest.

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