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Nonafluorobutanesulfonyl Azide: A Shelf-Stable Diazo Transfer Reagent for the Synthesis of Azides from Primary Amines

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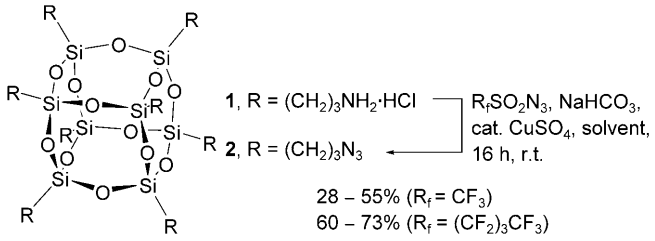
Abstract: Nonafluorobutanesulfonyl azide is an efficient, shelf-stable and cost-effective diazo transfer reagent for the synthesis of azides from primary amines. The reagent can also be successfully applied to the one-pot regioselective synthesis of 1,2,3-triazoles from primary amines by a sequential diazo transfer and azide–alkyne 1,3-dipolar cycloaddition process catalyzed by copper. The cycloaddition step can be conducted in an inter- or intramolecular way to afford 1,4- or 1,5-disubstituted triazoles, respectively. The atypical 1,5-regioselectivity under copper catalysis is a consequence of geometrical constraints of the amino-alkyne substrates used in the intramolecular version. Nonafluorobutanesulfonyl azide offers an advantageous alternative to the better known and most commonly used trifluoromethanesulfonyl azide.

Keywords: amines; azides; click chemistry; copper; diazo transfer

Introduction

Organic azides have found many important applications in organic synthesis,[1] chemical biology,[2] and materials science[3] thanks to their versatile chemistry. Thus, azides are readily reduced to amines, amides or carbamates, act as precursors for nitrenes and as radical traps, and undergo a variety of named reactions including 1,3-dipolar cycloadditions and rearrangement processes.[1] From a practical point of view, in addition to their widely recognized utility for the synthesis of 1,2,3-triazoles,[4] azides are convenient and atom-economic protecting groups for primary amines[5,6,7] and have found use as photoaffinity reagents for biomolecules[8] and as bioorthogonal chemical reporters in biological systems.[2,9] Although azides are most commonly prepared by nucleophilic substitution of an appropriate leaving group by the azide anion, this approach is sometimes compromised by competing elimination processes or by poor stereochemical control. An alternative and widely used approach is the diazo transfer reaction of primary amines with trifluoromethanesulfonyl azide (triflyl azide, TfN_3). This reaction takes place under mild conditions, with complete retention of configuration of the starting amine and has wide functional group compatibility. The method was originally described by Cavender and Shiner[5] in 1972 and was applied to amino acids nine years later,[10] but it did not found wider use until the early 1990s, when Vasella et al.[6] introduced it into carbohydrate chemistry. Over the years, the original experimental procedure has experienced some improvements, including the introduction of transition metal catalysts[7] and the substitution of dichloromethane with other solvents in the preparation of the TfN_3 reagent to avoid the adventitious formation of potentially explosive azidochloromethane and diazidomethane.[11] In spite of these developments, the use of TfN_3 as a diazo transfer reagent still suffers from several serious drawbacks. First, neat TfN_3 is an unstable and explosive compound that has to be prepared prior to use and should always be handled in solution.[5] In addition, the reagent is obtained from the rather costly trifluoromethanesulfonic anhydride and sodium azide[5] in variable yields and, accordingly, it is usually employed in large excess since it is cumbersome to determine its exact concentration in the crude solution.

In a recent project, we needed to prepare octakis(3-azidopropyl)octasilsesquioxane (**2**) starting from



Scheme 1. Synthesis of octa-azide **2** using TfN_3 and NfN_3.

commercially available octakis(3-aminopropyl)octasilsesquioxane octa-hydrochloride (**1**) by employing a diazo transfer approach (Scheme 1).[12] We hoped that the mild conditions of the diazo transfer process would prevent nucleophile-induced cage rearrangements[13] that were expected to occur in alternative routes to **2** using nucleophilic substitution reactions with azide anion.[14] Compound **1**, containing eight amino groups, provided a stringent test for the efficiency of the diazo transfer process. The moderate and variable yields of **2** that we obtained using TfN_3, together with the hazards and high cost of the reagent required for our gram-scale experiments prompted us to investigate safer and less costly options. In view of the known empirical relationship between explosiveness and nitrogen relative content of organic azides,[1b,c,15] we reasoned that higher molecular weight polyfluoroalkylsulfonyl azides could be safer alternatives to TfN_3 while holding a similar or even increased reactivity.[16] Among the commercially available polyfluoroalkylsulfonic acid derivatives, nonafluorobutanesulfonyl fluoride (nonaflyl fluoride, NfF)[17] is a bulk product that is remarkably cheaper than common triflating reagents. Reacting NfF with sodium azide in MeOH readily affords nonaflyl azide (NfN_3) in good yield.[18] This reagent is a colorless liquid with a characteristic pungent odor resembling that of TfN_3 and is stable at room temperature as a neat reagent, with a reported decomposition temperature of around 120 °C.[18b] Zhu et al. have studied the reactions of NfN_3 with electron-rich alkenes,[19] aromatic compounds,[20] and nitrogen,[21] phosphorus,[18b,c] and sulfur[18b,c] nucleophiles. However, at the onset of our work, there was only a single example reported in the literature on the use of NfN_3 for the synthesis of an organic azide from a primary amine.[22]

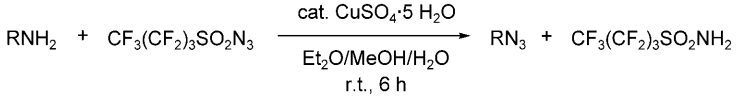
In our previous work,[12] we found that NfN_3 afforded higher and more reproducible yields of **2** (60–73%, which accounts for >94% yield per amino group) than TfN_3, under otherwise similar reaction conditions (Scheme 1). In order to assess the efficiency and general utility of NfN_3 as an advantageous and safer alternative to TfN_3 for the preparation of organic azides, we have now extended this study to a diverse set of amines, including simple alkylamines, arylamines, amino acids, hexosamines, and complex aminoglycosides.

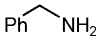
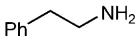
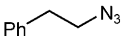
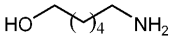
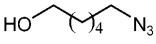
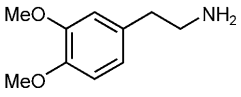
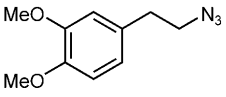
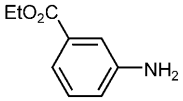
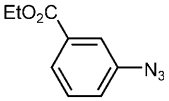
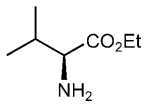
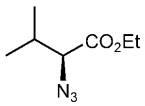
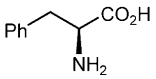
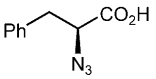
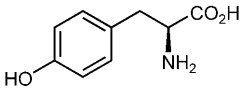
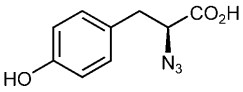
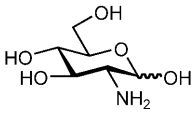
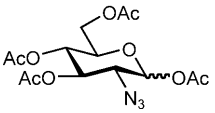
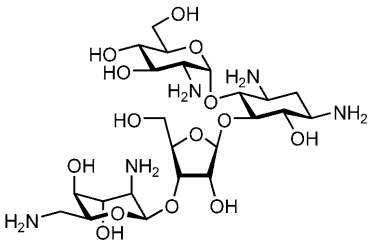
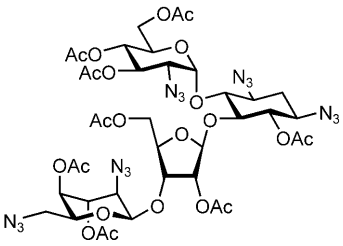
Results and Discussion

We prepared NfN_3 in *ca.* 20 to 40-gram batches following the described procedure.[18b,c] Although it has been reported that NfN_3 can be safely distilled under vacuum,[18a,c] the crude product was pure enough for our purposes as obtained, after drying over anhydrous Na_2SO_4. This reagent can be kept at 4 °C for months without any observable decomposition. For the diazo transfer reaction, a small excess (1.2–1.5 equivalents) of NfN_3 was added to a solution of the amine, a catalytic amount of $CuSO_4 \cdot 5H_2O$ (0.1 equivalent), and an excess of $NaHCO_3$ (4 equivalent) in a homogeneous $Et_2O/MeOH/H_2O$ (1:3:1) solvent mixture at room temperature. The reactions were usually complete after 1–6 h as judged by TLC analysis. The azide was isolated by liquid-liquid extraction of the crude reaction mixture with CH_2Cl_2, followed by repeated washing (5×) of the organic phase with a saturated aqueous solution of $NaHCO_3$ to remove the nonafluorobutanesulfonamide by-product. Residual nonafluorobutanesulfonamide was completely removed by sublimation during the concentration of the crude material at reduced pressure. This simple work-up afforded in most cases analytically pure products that did not required further purification. To facilitate isolation, azides derived from D-glucosamine and neomycin were peracetylated *in situ* by treating the concentrated crude reaction mixture with an excess of acetic anhydride in pyridine (Table 1, entries 9 and 10). Isolated yields of azides were good to excellent in all cases and compared favorably to those reported in the literature for the same substrates using TfN_3.

To further illustrate the versatility of NfN_3 as an efficient reagent for the preparation of azides, we also assayed its performance in sequential one-pot diazo transfer followed by intermolecular copper-catalyzed azide–alkyne 1,3-dipolar cycloaddition, as recently described for TfN_3.[23] Both aliphatic (Table 2, entries 1–3) and aromatic amines (Table 2, entries 4, 5) performed equally well in this transformation to give the expected 1,4-disubstituted 1,2,3-triazole products regioselectively and in good overall yields. The methodology could also be applied to intramolecular Huisgen cycloadditions (Scheme 2).[24] We selected two 2-(prop-2-yn-1-yloxy)anilines **10a**, **b** as substrates that could be readily prepared from the corresponding 2-nitrophenols. Due to geometrical constraints, the intramolecular 1,3-dipolar cycloaddition afforded only the corresponding 1,5-disubstituted tricyclic triazoles **11a**, **b**. We could not detect the presence of cyclic dimeric products or of higher oligomers in the ^1H NMR spectra of the crude reaction mixtures. Overall yields

Table 1. Synthesis of azides from primary amines with nonaflyl azide.



Entry	Substrate		Product		Yield [%][a]
1	**3a**		**4a**		91
2	**3b**		**4b**		88
3	**3c**		**4c**		97
4	**3d**		**4d**		94
5	**3e**		**4e**		86
6	**3f**		**4f**		89
7	**3g**		**4g**		90
8	**3h**		**4h**		85
9	**3i**		**4i**		74[b]
10	**3j**		**4j**		72[b]

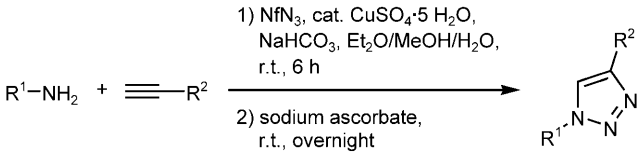
[a] Yield of pure product after simple extractive work-up (see text).
[b] Overall yield after conventional acetylation of the crude azide with an excess of Ac_2O in pyridine at room temperature followed by column chromatography purification (see Supporting Information).

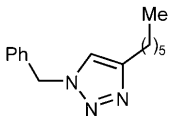
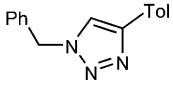
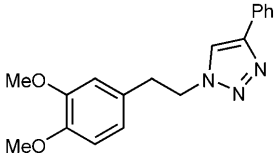
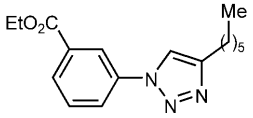
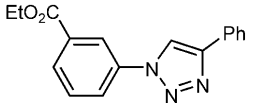
were *ca.* 20% higher in these two examples when the diazo transfer reaction was performed in the absence of copper catalyst, which required an extended reaction time, using CH_2Cl_2 instead of Et_2O in the solvent mixture. When the diazo transfer was complete, addition of $CuSO_4$/sodium ascorbate triggered the intramolecular Huisgen cycloaddition at room temperature, confirming that these were in fact Cu(I)-catalyzed cycloadditions in spite of their atypical regioselectivity.

Conclusions

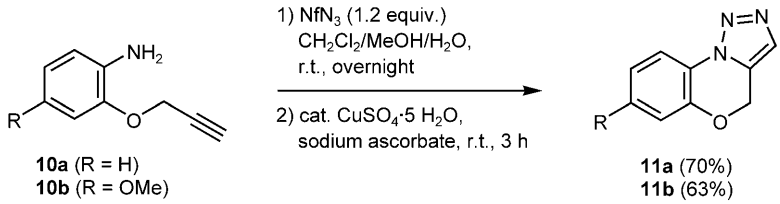
In summary, we have shown that nonafluorobutanesulfonyl azide is a shelf-stable and cost-effective diazo transfer reagent for the efficient synthesis of azides from primary amines. In most cases, the resultant azides can be readily isolated in pure form and in good yield after a simple extractive work-up that avoids chromatographic purification. The reagent has also proven its utility in the one-pot regioselective synthesis of 1,2,3-triazoles from primary amines by a sequential diazo transfer and azide–alkyne 1,3-dipolar cycloaddition process catalyzed by copper. This one-pot procedure can be applied to amino-alkynes to

Table 2. Synthesis of triazoles from primary amines by one-pot diazo transfer and intermolecular Huisgen 1,3-dipolar cycloaddition using nonaflyl azide.



Entry	R^1NH_2	R^2	Product		Yield [%][a]
1	**3a**	$(CH_2)_5CH_3$	**5**		83
2		*p*-Tol	**6**		77
3	**3d**	Ph	**7**		62
4	**3e**	$(CH_2)_5CH_3$	**8**		80
5		Ph	**9**		66

[a] Overall isolated yield.



Scheme 2. Synthesis of triazoles from primary amines by one-pot diazo transfer and intramolecular Huisgen 1,3-dipolar cycloaddition using nonaflyl azide

afford the corresponding 1,5-disubstituted 1,2,3-triazoles, due to geometrical constraints. Nonaflyl azide is an advantageous alternative to the better known and most commonly used triflyl azide. Together with the recently described imidazole-1-sulfonyl azide,[25] the nonaflyl analogue is an interesting addition to the growing arsenal of efficient and shelf-stable diazo transfer reagents. Investigations on other synthetic applications of this compound are currently underway in our laboratory.

Experimental Section

General Procedure for Diazo Transfer Reactions

To a solution of the corresponding amine **3** (0.6 mmol) in water (0.8 mL) was added in sequence MeOH (2.2 mL), $NaHCO_3$ (0.201 g, 2.4 mmol), a solution of nonafluorobutanesulfonyl azide (0.295 g, 0.9 mmol) in Et_2O (1.2 mL) and $CuSO_4{\cdot}5\,H_2O$ (14 mg, 0.06 mmol). The reaction mixture was stirred at room temperature for 6 h. The mixture was concentrated at reduced pressure, CH_2Cl_2 (15 mL) was added, and the resultant solution was washed with a saturated aqueous solution of $NaHCO_3$ (5×10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and concen-

trated under reduced pressure. The corresponding azide **4** was obtained in pure form without any further purification.

General Procedure for One-Pot Diazo Transfer and Intermolecular 1,3-Dipolar Huisgen Cycloaddition Reactions

To a solution of the corresponding amine **3** (0.6 mmol) in water (0.8 mL) was added in sequence MeOH (2.2 mL), $NaHCO_3$ (0.201 g, 2.4 mmol), a solution of nonafluorobutanesulfonyl azide (0.295 g, 0.9 mmol) in Et_2O (1.2 mL) and $CuSO_4 \cdot 5H_2O$ (14 mg, 0.06 mmol). The reaction mixture was stirred at room temperature for 6 h. Then, a terminal alkyne (0.06 mL, 0.65 mmol) and sodium ascorbate (178 mg, 0.9 mmol) were added and the reaction mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure, CH_2Cl_2 (15 mL) was added, and the resultant solution was washed with a saturated aqueous solution of $NaHCO_3$ (4×10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford the corresponding triazole **5**–**9**.

General Procedure for One-Pot Diazo Transfer and Intramolecular 1,3-Dipolar Huisgen Cycloaddition Reactions

To a solution of the corresponding amine **10** (0.6 mmol) in water (0.8 mL) was added in sequence MeOH (2.2 mL), $NaHCO_3$ (0.201 g, 2.4 mmol), a solution of nonafluorobutanesulfonyl azide (0.295 g, 0.9 mmol) in CH_2Cl_2 (1.2 mL). After stirring the reaction mixture at room temperature for 12 h, $CuSO_4 \cdot 5H_2O$ (14 mg, 0.06 mmol) and sodium ascorbate (178 mg, 0.9 mmol) were added and the reaction was stirred at room temperature for 3 h. The mixture was concentrated under reduced pressure, CH_2Cl_2 (15 mL) was added, and the resultant solution was washed with a saturated aqueous solution of $NaHCO_3$ (4×10 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford the corresponding tricyclic triazole **11**.

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