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An Efficient, Inexpensive, and Shelf-Stable Diazotransfer Reagent: Imidazole-1-sulfonyl Azide Hydrochloride

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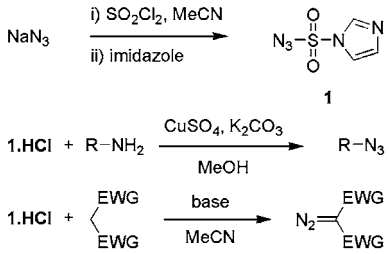
ABSTRACT

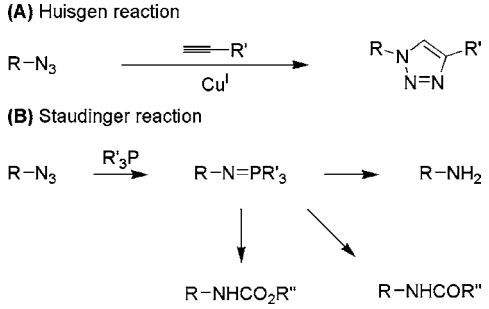


The design and synthesis of a new diazotransfer reagent, imidazole-1-sulfonyl azide hydrochloride, are reported. This reagent has proven to equal triflyl azide in its ability to act as a "diazo donor" in the conversion of both primary amines into azides and activated methylene substrates into diazo compounds. Crucially, this reagent can be prepared in a one-pot reaction on a large scale from inexpensive materials, is shelf-stable, and is conveniently crystalline.

In recent times, organic azides have experienced something of a renaissance, owing, in no small part, to the immense popularity of the Cu^{I}-catalyzed reaction between azides and terminal alkynes (Scheme 1A).[1] Indeed, Sharpless and Fokin, in their seminal paper on this reaction, describe the reluctance of modern organic chemists to embrace the azide moiety as "azidophobia".[2] Fueled by the findings of this same publication, one could argue the chemistry community presently experiences quite the opposite condition—"azidophilia".

The utility of the azide moiety is not limited to the synthesis of 1,2,3-triazoles. It also provides great service as a latent amino group. As a protecting group, azides circumvent many of the problems encountered with amides and carbamates, as well as providing the option of a mild reduction, via a Staudinger phosphazene, to give a primary amine,[3] amide,[4] or carbamate (Scheme 1B).[5]

Scheme 1. Useful Reactions of Organic Azides



Indeed, such is the reliability of the Huisgen and Staudinger reactions that they have found application in the study of biological systems, as exemplified by the work of Wong[6] and Bertozzi.[7]

(1) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51−68.
(2) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599.
(3) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353−1406.
(4) Bosch, I.; González, A.; Urpí, F.; Vilarrasa, J. *J. Org. Chem.* **1996**, *61*, 5638−5643.
(5) Ariza, X.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1999**, *40*, 7515−7517.

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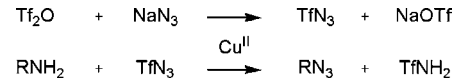
Most commonly, an azide group is introduced into a molecule by the formation of a C−N bond, usually by the nucleophilic displacement of a nucleofuge by an azide ion. Although largely successful, this approach can, in some systems, lead to the formation of elimination products or products with incorrect stereochemical configuration.

In contrast to the former approach is the diazotransfer reaction. This process utilizes trifluoromethanesulfonyl azide (TfN_3) as a "diazo donor" in the Cu^{II}-catalyzed conversion of an existing primary amine into an azide (Scheme 2).[8] The

Scheme 2. TfN_3 in the Diazotransfer Reaction



elegance of this process lies in its mild reaction conditions, high yields, and, crucially, the preservation of any pre-existing stereochemistry.

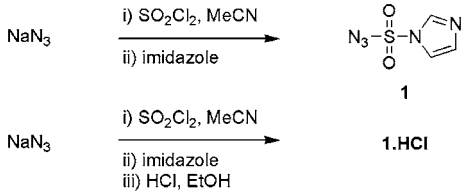
However, this process is not without its problems. The explosive nature of neat TfN_3 and its relatively poor shelf life necessitate its preparation in solution prior to use.[9] Furthermore, inconsistent yields in the preparation of TfN_3 mean that the solution must either be standardized or used in a liberal excess. The removal of trifluoromethanesulfonamide from polar products has in the past also required specialized workup procedures.[10] Perhaps most significantly, the expense of trifluoromethanesulfonic anhydride, used in the preparation of TfN_3, prohibits the deployment of this reaction on a large scale. To circumvent these problems and establish the diazotransfer reaction as a commonplace and industrially useful synthetic transformation, a cheap, robust, and safe alternative to TfN_3 is required.

The challenge in designing such an alternative lies in finding an electron-withdrawing group capable of replacing the trifluoromethanesulfonyl moiety. Simple arylsulfonyl azides have, in the past, proven to be inadequate,[11] and although other fluoroalkylsulfonyl groups are available, they would do little to address the aforementioned shortcomings of TfN_3.

Hanessian and Vatèle first demonstrated the imidazole-1-sulfonate (imidazylate) group's capacity as an excellent nucleofuge.[12] Imidazylates exhibit very similar reactivity to trifluoromethanesulfonates but often enjoy a longer shelf life, are a great deal less expensive to prepare, and produce a hydrolytically labile counterion.[12] We envisaged that imidazole-1-sulfonyl azide **1** would mimic TfN_3 in its ability to act as a diazotransfer reagent but might also be less costly to prepare, more stable (hopefully crystalline), and produce more easily removed byproducts.

The synthesis of **1** was easily accomplished by the addition of two mole equivalents of imidazole to chlorosulfonyl azide, preformed in situ by the reaction of equimolar quantities of sodium azide and sulfuryl chloride in acetonitrile.[13] Subsequent aqueous workup and flash chromatography afforded **1** as a colorless liquid in good yield (72%) (Scheme 3).

Scheme 3. Synthesis of **1** and **1·HCl**



To assess the ability of **1** to behave as a diazo donor, D-glucosamine hydrochloride was treated with **1** under typical diazotransfer conditions to give, following acetylation, the azide (1,3,4,6-tetra-*O*-acetyl-2-azido-2-deoxy-D-glucose) in good yield (entry 1, Table 1).

This result, a boon though it was, failed to satisfy us in one respect: to deliver a crystalline diazotransfer reagent, desired for reasons of stability, ease of purification, and convenience of measure. Fortuitously, the hydrochloride of **1** proved to be a colorless crystalline solid that, not surprisingly, gave the same reaction with D-glucosamine hydrochloride as observed for **1** (entry 1, Table 1). Modification of the synthesis of **1** permitted the one-pot preparation of **1·HCl** on a large scale, without the need for chromatography, in good yield and high purity (Scheme 3).

Impact tests, vigorous grinding, and prolonged heating (at 80 °C) of **1·HCl** failed to invoke any explosive reaction. Heating **1·HCl** above its melting point resulted in the slow evolution of gas, presumably dinitrogen, to give a yellow liquid, most likely the corresponding diazene. Differential scanning calorimetry revealed this to be an exothermic process (Figure 1). Further strong heating (>150 °C) of the

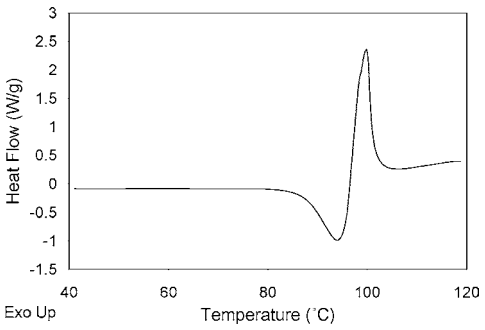
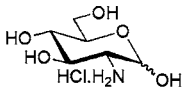
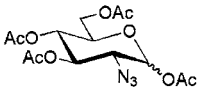
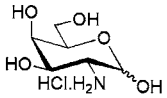
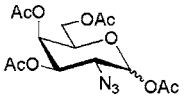
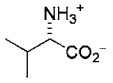
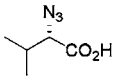
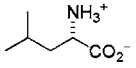
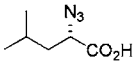
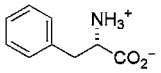
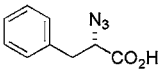
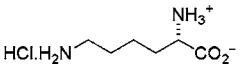
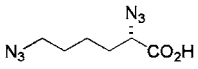
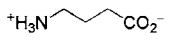
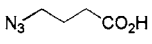
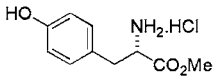
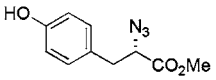
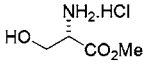
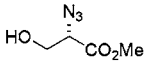
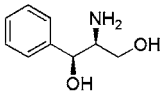
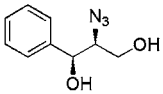
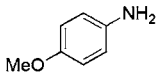
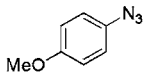
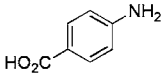
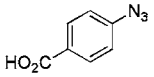
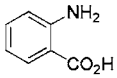
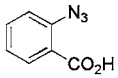


Figure 1. Differential scanning calorimetry of **1·HCl**.

(6) Sawa, M.; Hsu, T.-L.; Itoh, T.; Sugiyama, M.; Hanson, S. R.; Vogt, P. K.; Wong, C.-H. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 12371−12376.
(7) Vocadlo, D. J.; Bertozzi, C. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 5338−5342.
(8) (a) Cavender, C. J.; Shiner, V. J. *J. Org. Chem.* **1972**, *37*, 3567−3569. (b) Vasella, A.; Witzig, C.; Chiara, J.-L.; Martin-Lomas, M. *Helv. Chim. Acta* **1991**, *74*, 2073−2077. (c) Alper, P. B.; Hung, S.-C.; Wong, C.-H. *Tetrahedron Lett.* **1996**, *37*, 6029−6032.
(9) Nyffeler, P. T.; Liang, C.-H.; Koeller, K. M.; Wong, C.-H. *J. Am. Chem. Soc.* **2002**, *124*, 10773−10778.
(10) Lundquist, J. T., IV; Pelletier, J. C. *Org. Lett.* **2001**, *3*, 781−783.
(11) Araki, K.; Hashimoto, H.; Yoshimura, J. *Carbohydr. Res.* **1982**, *109*, 143−160.

Table 1. Synthesis of Azides from Primary Amines Utilizing **1** and **1·HCl**[a]

entry	substrate	product	time [lit.][c] (h)	yield [lit.][c] (%)
1[b]			2 [12][14]	92 [94][14]
2			2 [12][14]	87 [95][14]
3			12 [12][10]	84 [75][10]
4			12 [12][10]	85 [68][10]
5			12 [12][10]	75 [62][10]
6			12	66
7			12	72[d]
8			6	90
9			6 [2][15]	83 [62][15]
10			4	91
11			4 [0.6][e, 16]	78 [90][16]
12			12 [3][e, 16]	85 [88][16]
13			12	83

[a] In a typical experiment, **1·HCl** (1.2 mmol) was added to a stirred suspension of the amine or its hydrochloride (1.0 mmol), potassium carbonate (2.0 mmol), and copper(II) sulfate pentahydrate (10 μmol, 1 mol %) in methanol (5 mL). Upon completion of the reaction (TLC), the mixture was concentrated. For non-carbohydrate substrates (entries 3−13), a workup and flash chromatography furnished the corresponding azide. For carbohydrate substrates (entries 1 and 2), acetic anhydride (8 mmol) was added to the residue in pyridine (5 mL). Upon completion of the reaction (TLC), the mixture was concentrated; a workup and flash chromatography then furnished the corresponding peracetylated azides. [b] The reaction was performed independently with **1** and **1·HCl** to give indentical results. [c] For the comparable reaction with TfN_3, where such a value is available. [d] The product is volatile, resulting in reduced yields. [e] This literature value was obtained using 15 mol % of Cu^{II} catalyst as opposed to the 1 mol % used here.

residue resulted in violent decomposition. We thus advocate the use of **1·HCl** at temperatures well below its decomposition point, preferably at room temperature, in line with accepted experimental procedures employing TfN_3.

Various amines were converted into the corresponding azides by the action of **1·HCl** (Table 1). In general and where possible, yields and reaction times compared favorably to those obtained in the literature with TfN_3.[10,14−16] The results presented in Table 1 clearly demonstrate the reliability of **1·HCl** to perform the diazotransfer reaction in good to excellent yield and reasonable reaction time, with good

(12) (a) Hanessian, S.; Vatèle, J.-M. *Tetrahedron Lett.* **1981**, *22*, 3579−3582. (b) Vatèle, J.-M.; Hanessian, S. *Tetrahedron* **1996**, *52*, 10557−10568.

(13) Griffiths, J. *J. Chem. Soc. C* **1971**, 3191−3195.

(14) Yan, R.-B.; Yang, F.; Wu, Y.; Zhang, L.-H.; Ye, X.-S. *Tetrahedron Lett.* **2005**, *46*, 8993−8995.

(15) Manabe, S.; Sakamoto, K.; Nakahara, Y.; Sisido, M.; Hohsaka, T.; Ito, Y. *Bioorg. Med. Chem.* **2002**, *10*, 573−581.

(16) Liu, Q.; Tor, Y. *Org. Lett.* **2003**, *5*, 2571−2572.

functional group tolerance and a propensity to react even with electron-deficient amines.

Although Cu^{II} salts have emerged as the catalysts of choice for the diazotransfer reaction with TfN_3, the reaction is also catalyzed by Ni^{II} and Zn^{II} salts.[8c] Qualitative experiments conducted on D-glucosamine hydrochloride indicated that the diazotransfer reaction utilizing **1·HCl** is catalyzed by Cu^{II}, Ni^{II}, Zn^{II}, and Co^{II} salts (1 mol % of $MCl_2 \cdot nH_2O$).

As a diazo donor, TfN_3 has also been used in the preparation of various diazo compounds from substrates containing activated methylene groups.[17] Diazo compounds have proven to be of use in cyclopropane synthesis, X−H insertion reactions (where X is C, O, N, S, P, or Si), and ylide preparation.[18]

Table 2. Synthesis of Some Diazo Compounds Utilizing **1·HCl**[a]

R	time (h)	yield [lit.][b] (%)
CO_2Et	16	65 [56][17]
C(O)Me	16	59
CN	9	61 [79][17]
SO_2Ph	48	–[c]
$P(O)(OEt)_2$	48	–[c]

[a] In a typical experiment, the substrate (1.0 mmol), **1·HCl** (1.2 mmol), and a non-nucleophilic base (5.0 mmol) (pyridine or potassium carbonate) were stirred in acetonitrile. Upon completion of the reaction (TLC), the mixture was concentrated, and a workup and flash chromatography furnished the diazo compound. [b] For the comparable reaction with TfN_3, where such a value is available. [c] No reaction was observed (TLC and NMR).

Preliminary investigations into the use of **1·HCl** in the preparation of diazo compounds were conducted, the results of which are presented in Table 2. It should be noted that the volatile nature of the products resulted in only moderate yields, not truly representative of the reaction's efficacy.

In conclusion, an inexpensive, shelf-stable, and efficient alternative to TfN_3 in the diazotransfer reaction has been designed and prepared in a simple one-pot procedure. The utility of this new reagent, imidazole-1-sulfonyl azide hydrochloride **1·HCl**, in the conversion of a diverse range of amines into the corresponding azides, with excellent results, has been demonstrated. Further, the preparation of several diazo compounds using **1·HCl** has been accomplished.

Acknowledgment. E.D.G.-B. would like to thank The University of Western Australia for a Hackett postgraduate scholarship.

Supporting Information Available: All experimental procedures and characterization data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Wurz, R. P.; Lin, W.; Charette, A. B. *Tetrahedron Lett.* **2003**, *44*, 8845−8848.

(18) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; John Wiley & Sons: New York, 1998.