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An Updated Synthesis of the Diazo-Transfer Reagent Imidazole-1-sulfonyl Azide Hydrogen Sulfate

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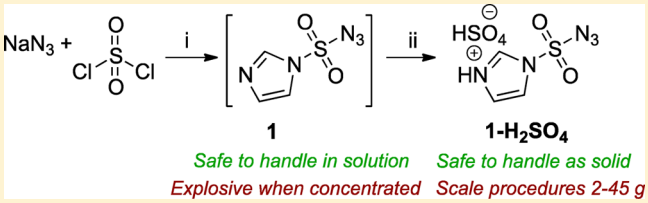
Supporting Information

ABSTRACT: Imidazole-1-sulfonyl azide and salts thereof are valuable reagents for diazo-transfer reactions, most particularly conversion of primary amines to azides. The parent reagent and its HCl salt present stability and detonation risks, but the hydrogen sulfate salt is significantly more stable. An updated procedure for the large-scale synthesis of this salt avoids isolation or concentration of the parent compound or HCl salt and will facilitate the use of hydrogen sulfate salt as the reagent of choice for diazo transfer.



The conversion of primary amines to azides via diazo-transfer is an important reaction in organic synthesis. Azides are frequently used as reagents in CuAAC click reactions[1] with applications in bioorthogonal click chemistry,[2] peptide conjugation,[3] and polymerization processes.[4] They are also utilized as amine masking groups, in carbohydrate chemistry, including for 2-amino pyranoses[5] and oligonucleotide chemistries.[6] Diazo-transfer reagents have also been applied during total syntheses such as (−)-ephedradine A[7] and (±)-aspidophytine[8] to generate intermediary diazo functional groups. Conversion of the product azides to the parent amine is usually achieved under reductive conditions or using Staudinger ligation.[9] Owing to this convenient masking and unmasking of an ambient nucleophile and the broad utility of organo-azides, there is ongoing interest in the synthesis and application of diazo-transfer reagents. However, their use has historically been tainted by concerns regarding the chemical stability of the reagents and processes required to prepare them.

Cavender and Shiner first reported the use of trifluoromethanesulfonyl azide (TfN_3) as an organic-soluble diazo-transfer reagent more than 40 years ago.[10] This quickly became the commonly chosen reagent for such transformations, and it is still widely used in syntheses today.[11,12] However, its preparation requires the use of the expensive and toxic triflic anhydride.[13] Additionally, TfN_3 is renowned for hazards during its preparation and storage, as it is highly explosive. As such, it is not available commercially and is usually necessarily prepared immediately prior to use. If storage is required, then dilute solutions are necessary.[14] Convenient access toward less-hazardous and shelf-stable diazo-transfer reagents is thus highly desirable. Some progress was made toward this with the development of nonafluorobutanesulfonyl azide, which increases molecular weight and overall safety, but further improvement of this important reagent class is preferable.[15]

Imidazole-1-sulfonyl azide (**1**), first reported by Goddard-Borger and Stick, is an alternative diazo-transfer source with similar reactivity to TfN_3 (Scheme 1A).[16] This reagent has a longer shelf life than TfN_3, and its cost of preparation is significantly lower. However, purification of **1** requires concentration *in vacuo* and flash chromatography, introducing the risk of friction-induced explosion in addition to concentration-related instability.[16]

An updated synthesis of **1** by Ye et al. prevented the formation of hydrazoic acid or sulfuryl diazide by using methyl trifluoromethanesulfonate in a two-step process, significantly increasing the safety of the process and allowing its formation on 100-g scale.[18] Unfortunately, the approach required HPLC monitoring and immediate use of the reagent *in situ*.[18]

Seeking a more stable form of **1**, Goddard-Borger and Stick further reported a one-pot formation of its hydrochloride salt (**1-HCl**) as a crystalline solid that could be safely handled when freshly prepared (Scheme 1B).[16] This "shelf-stable" reagent gained popularity and has been used across a wide range of synthetic applications. The numerous uses include the formation of clickable scaffolds to link biomolecules,[19] the synthesis of azide-containing intermediates for 4,6-disubstituted aminoglycoside antibiotics,[11] and introduction of clickability into the synthesis of soft bioisosteric supramolecular materials.[20] Our lab has further reported the application of **1-HCl** for 50 g batch-scale conversion of 2-deoxy-2-amino sugars to 2-deoxy-2-azido sugars.[5]

However, a report in the literature revealed an explosion had taken place during the formation of **1-HCl**.[21] It was determined that the concentration of mother liquors following crystallization is hazardous, with explosive byproducts sulfonyl diazide

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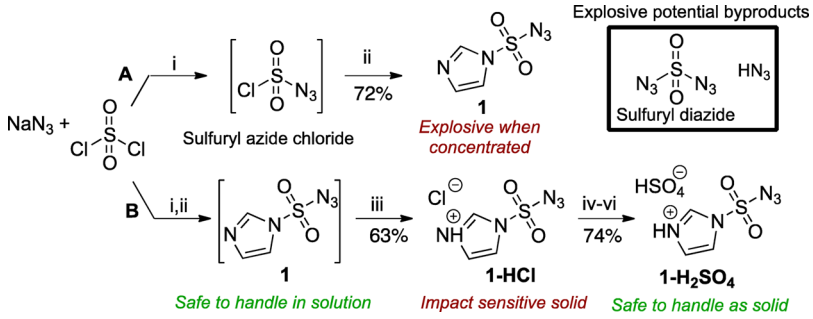
Scheme 1. Reported Syntheses of Imidazole-1-sulfonyl Azide,[17] HCl, and H_2SO_4 Salts[a]



[a]Reagents and conditions: (i) MeCN; (ii) ImH, MeCN; (iii), HCl, EtOH.[16] (iv) 1-HCl partitioned EtOAc/sat. aq. $NaHCO_3$; (v) EtOAc layer separated; (vi) H_2SO_4.[22] Both syntheses have the potential to generate sulfuryl diazide and hydrazoic acid.[22]

or hydrazoic acid potentially present in solution.[21] Furthermore, it was reported that **1-HCl** is hygroscopic and over time decomposes to release hydrazoic acid.[21] Impact studies of **1-HCl** found that it has similar impact sensitivity to the highly explosive RDX, requiring caution during handling and is no longer considered safe for transport.[22]

Alternative salt forms of **1** have been synthesized which display similar reactivity toward amines, but with a range of different explosive sensitivities and shelf stabilities.[22] The sulfate salt of **1** (**1-H_2SO_4**) has a high decomposition temperature of 131 °C, is insensitive to drophammer impact, and has low electrostatic discharge and friction sensitivities, making it significantly safer to handle than **1-HCl**.[22] In addition, while **1-HCl** was observed to discolor within weeks of formation, suggesting release of hydrazoic acid, **1-H_2SO_4** was reported as stable under ambient conditions for several months.[22]

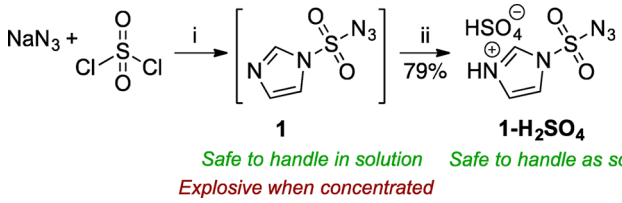
With its increased stability, **1-H_2SO_4** use has seen increasing adoption, including for isotopically labeled mechanistic studies revealing the reagent indeed acts via a diazo-transfer mechanism.[23] It has further been used in the synthesis of azide-functionalized units toward generation of peptidomimetic scaffolds[24] to label natural products for solid support anchoring[25] and synthesis of azides employed in the construction of bis-triazole pyridyl ligands.[26]

The reported synthesis of **1-H_2SO_4** is a two-step procedure first requiring the synthesis and isolation of **1-HCl**, followed by the dissolution of this salt in saturated aqueous sodium bicarbonate, partitioning with EtOAc and treating the organic layer with H_2SO_4 to form the desired sulfate (Scheme 1B).[22] While the reagents used for this process are relatively inexpensive, the yield of **1-H_2SO_4** is 46% over two processes from **1** and requires isolation of **1-HCl**.[22] We thus sought to evaluate methods of synthesis for **1-H_2SO_4** which avoid isolation of the HCl salt and concurrently improve overall yield.

Our initial attempts toward synthesizing **1-H_2SO_4** focused primarily on safety aspects, modifying the workup and isolation procedures previously reported to avoid the handling of **1-HCl** as a solid or **1** as a concentrated solution. We found that **1** could be generated as a safely diluted solution at 2 M in acetonitrile and, following partitioning with saturated aqueous $NaHCO_3$ and extraction into EtOAc, **1-H_2SO_4** could be precipitated directly from the organic layer, thereby avoiding **1-HCl** (Scheme 2).

Our initial syntheses suspended NaN_3 at 1 mmol per mL in MeCN with cooling to 0 °C. Addition of sulfuryl chloride led to formation of the intermediate sulfuryl azide chloride and subsequent addition of imidazole to the suspension generated **1**

Scheme 2. Synthesis and Isolation of 1-H_2SO_4[17] *via in Situ* Salt Formation Avoiding Isolation or Concentration of Potentially Explosive Intermediates[a]



[a]Reagents and conditions: (i) (1) MeCN and/or EtOAc; (2) ImH, MeCN; (ii) (1) **1** partitioned EtOAc/sat. aq. $NaHCO_3$; (2) EtOAc layer separated; (3) H_2SO_4.

in MeCN (effective 1 M solution for full conversion). The resulting suspension was diluted by adding saturated aqueous $NaHCO_3$ (~3 volume equivalents; also destroying hydrazoic acid) and partitioned after addition of EtOAc using half the original volume of MeCN. To the resulting separated and dried imidazole-1-sulfonyl azide solution, 1 equiv of *c*.H_2SO_4 was added directly. The resulting precipitate of **1-H_2SO_4** was collected from solution affording the desired product on 25 g batch scale over two steps, having avoided the isolation and handling of either **1** or **1-HCl** (Table 1, entry 1).

Table 1. Optimizing Synthesis of 1-H_2SO_4[a]

entry	method	NaN_3 mmol/mL of reaction solvent	EtOAc/MeCN	yield (%)
1	A	1	1:2[b]	41
2	A	1	2:1[b]	12
3	A	2	2:1[b]	60
4	B	2	2:1[c]	59
5	B	2	3:1[c]	79
6	B	2	1:0[c]	78

[a]All reactions were conducted for 24 h. [b]Method A: reaction conducted in neat acetonitrile with subsequent EtOAc extraction. [c]Method B: reaction conducted in MeCN/EtOAc solvent mixture or neat EtOAc without organic extraction step.

Hypothesizing that some product loss could be due to the aqueous miscibility of MeCN, we investigated the effect of the EtOAc/aqueous ratio upon extraction. Increasing the volume of EtOAc by 4-fold during the extraction process (Table 1, entry 2) led to the resulting organic solution being too dilute to enable adequate precipitation of **1-H_2SO_4**, and thus causing a significant drop in isolated yield. However, by doubling the

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original reaction concentration of NaN_3 (to 2 mmol per mL) in MeCN and then using the same 2:1 ratio of EtOAc extractant to MeCN reaction solution, led to an increased yield of 60% (Table 1, entry 3).

Acetonitrile is generally the solvent of choice for the synthesis of sulfonyl azides due to incompatibility or insolubility issues with other common solvents.[27] While EtOAc was originally assessed as a solvent for sodium azide reactions over 40 years ago, the low solubility of NaN_3 and resulting long reaction times, and/or necessary addition of DMF as a solvent catalyst, have discouraged use.[27] Prior synthesis of imidazole-1-sulfonyl azide reagents has thus unsurprisingly been to date contingent on use of MeCN, and not EtOAc, as solvent.[16] However, given the enhanced yields we obtained using EtOAc as an extraction solvent (*vide supra*) we decided to revisit the possible use of EtOAc as a solvent/cosolvent for the synthesis of imidazole-1-sulfonyl azide, proposing to determine if the explicit extraction step above could then be circumvented. Thus, different EtOAc/MeCN ratios were evaluated as the reaction solvent system (Table 1, Method B), with aqueous wash/partition workup, but no additional organic extraction then employed.

Using EtOAc as a reaction cosolvent rather than extractant in the optimum process from those evaluated using an extraction-based work up (Table 1, entry 3), gave essentially the same yield outcome (Table 1, entry 4) on 5 g sodium azide scale. Furthermore, it was found that increasing the EtOAc/MeCN ratio led to significantly increased overall isolated yields. Using only EtOAc as reaction solvent, **1-H_2SO_4** was isolated in a significantly increased yield of 78 ± 4% (Table 1, entry 6). It was thus concluded that acetonitrile could be avoided altogether, and that the reaction can be run effectively in pure EtOAc.

To study the applicability of this procedure across various scales, reactions utilizing Method B were conducted with differing amounts of sodium azide. Due to the product being readily storable, we felt most laboratories would not benefit from subgram production, so the smallest scale we evaluated used 1.0 g of sodium azide, which yielded 2.1 g of **1-H_2SO_4** (51%). On the larger scale, we felt an evaluation of 15 g of sodium azide could be safely duplicated in most laboratory environments, yielding 46.0 g of **1-H_2SO_4** (73%).

These reactions are reliable and reproducible, and the synthesis of **1-H_2SO_4** was safely conducted to provide tens of grams of this valuable reagent. Stored at 4 °C, the bulk of reagent prepared in this manner shows no discoloration or loss of reagent capability after 6 months. Use of **1-H_2SO_4** to duplicate literature reactions which had previously been conducted utilizing **1-HCl** yielded comparable results, verifying its ability as a diazo-transfer reagent (see Supporting Information).

CONCLUSIONS

The process for synthesis of **1-H_2SO_4** has been updated to avoid the handling of potentially explosive intermediates (**1** or **1-HCl**, as either a solid or concentrated solution) or byproducts. Furthermore, the overall yield of this important diazo-transfer reagent has been significantly increased (46%—78%) and optimized by replacement of MeCN as the reaction solvent with EtOAc. The method described above allows for synthesis, crystallization, and isolation of the shelf-stable salt **1-H_2SO_4**. We believe this process improvement will encourage the use of **1-H_2SO_4** as the reagent of choice when performing diazo-transfer reactions in organic synthesis.

EXPERIMENTAL SECTION

While this updated methodology significantly decreases the risk of explosion during preparation of imidazole-1-sulfonyl azide hydrogen sulfate, precaution should remain paramount. Blast shields should be used with any azide-reagent containing solution, and care should be taken to ensure the reaction remains free of water in acidic stages. Addition of imidazole should be under an inert atmosphere. Aqueous and organic wastes should be treated with 1.5 equiv of sodium nitrite and acidified with stirring to destroy azide-containing byproducts.

General Methods. All chemicals used were purchased from commercial sources without further purification. Conc. H_2SO_4 refers to standard grade concentrated H_2SO_4 from Fisher (18M, 95—98%). Solvents listed as "dry" were dried over molecular sieves in accordance with parameters established by Williams and Lawton.[28] ^1H NMR spectra were recorded at 400 MHz, and ^{13}C spectra, at 100 MHz, respectively. Chemical shifts (δ, in ppm) are standardized against the deuterated solvent peak. NMR data were analyzed using Nucleomatica iNMR software. ^1H NMR splitting patterns were assigned as follows: s (singlet), d (doublet), dd (doublet of doublets), or t (triplet). MALDI were obtained by using a MALDI-TOF mass spectrometer in reflectron mode. Infrared spectra were obtained by using an FT-IR instrument. Melting points were determined using a digital melting point apparatus and are uncorrected.

Imidazole-1-sulfonyl Azide Hydrogen Sulfate (1-H_2SO_4). *Method A.* Sodium azide (10.1 g, 156 mmol) was placed in a 250 mL round-bottomed flask with a stirrer bar. The flask was evacuated, a N_2 atmosphere was introduced, dry acetonitrile (78 mL) was added, and the resulting suspension was cooled to 0 °C. While the inert atmosphere was maintained, sulfuryl chloride (12.6 mL, 156 mmol) was then added dropwise over the course of at least 10 min with stirring, and the mixture was slowly warmed to room temperature and stirred for at least 17 h. The suspension was then recooled to 0 °C, and while the inert atmosphere was maintained, imidazole (20.2 g, 296 mmol) was added continuously over 10 min. The solution was stirred for at least 3 h at 0 °C, diluted with EtOAc (156 mL), and basified by addition of saturated aqueous $NaHCO_3$ (250 mL). The organic layer was then washed with water (250 mL), dried over $MgSO_4$, and filtered. This solution was then cooled to 0 °C and placed under a N_2 atmosphere, and conc. H_2SO_4 (3 mL, 156 mmol) was added dropwise over the course of 5 min. The mixture was gradually allowed to warm to room temperature, stirring vigorously. After 24 h, a colorless precipitate had formed. Vacuum filtration followed by a wash with a small amount of cooled EtOAc afforded white crystals which were left to dry for 15 min, then collected in a round-bottom flask, and dried under high vacuum to afford pure **1-H_2SO_4** (25.2 g, 93 mmol, 60%). The reagent was collected and stored under N_2 in the fridge. While discoloration of **1-H_2SO_4** has not been observed following its handling with metal utensils, plastic utensils are suggested as a precaution.

Method B. Sodium azide (5.0 g, 77 mmol) was placed in a 250 mL round-bottomed flask with a stirrer bar. The flask was evacuated, a N_2 atmosphere was introduced, dry EtOAc (77 mL) was added, and the resulting suspension was cooled to 0 °C. While the inert atmosphere was maintained, sulfuryl chloride (6.2 mL, 77 mmol) was then added dropwise over the course of at least 10 min with stirring, and the mixture was slowly warmed to room temperature and stirred for at least 17 h. The suspension was then recooled to 0 °C, and while the inert atmosphere was maintained, imidazole (10.0 g, 146 mmol) was added continuously over 5 min. The thick suspension was stirred for at least 3 h at 0 °C and then basified by addition of saturated aqueous $NaHCO_3$ (150 mL). The organic layer was then washed with water (150 mL) and dried over $MgSO_4$. This solution was filtered and cooled to 0 °C and placed under a N_2 atmosphere, and conc. H_2SO_4 (4.1 mL, 77 mmol) was then added dropwise over the course of 5 min. The mixture was gradually warmed to room temperature, stirring vigorously. After 30 min, a colorless precipitate had formed. Filtration followed by a wash with a small amount of cooled EtOAc afforded

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white crystals which were left to dry for 15 min, then collected in a round-bottom flask, and dried under high vacuum to afford pure **1-H_2SO_4** (16.2 g, 60 mmol, 78%). The reagent was collected and stored under N_2 in the fridge. While discoloration of **1-H_2SO_4** has not been observed following its handling with metal utensils, plastic utensils are suggested as a precaution.

^{1}H NMR (DMSO-d_6, 400 MHz) δ 14.29 (s, br, NH^+), 13.11 (s, HSO_4^-), 9.08 (s, CH), 8.08 (t, J = 1.7 Hz, CH), 7.52 (dd, J = 1.7, 0.8 Hz, CH); ^{13}C NMR (101 MHz; DMSO-d_6) δ 138.6, 128.0, 119.9 (as previously noted,[20] up to 10% decomposition occurs in DMSO as evidenced by additional peaks in both ^{1}H NMR [9.01 (s, br, CH), 7.61 (d, J = 0.8 Hz, CH)]; and ^{13}C NMR [134.8, 119.8]). m/z (MALDI) 294 (MNa^+, 100%), 335 ($[MeCN + MNa]^+$, 30%); FTIR (neat) ν_{max} 2176 (N_3), 1301 (asymm. S═O), 1125 (symm. S═O) cm^{-1}; Mp: 102−105 °C (Lit. 105−108 °C). Observed data match literature values.[20]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00177.

Copies of **1-H_2SO_4** ^{1}H and ^{13}C NMR, mass spectra, and FTIR. Stepwise procedure with accompanying color photographs following Method B to allow for ease of reproducibility with safety. Representative diazotransfer protocol utilizing **1-H_2SO_4** (PDF)

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Notes

The authors declare no competing financial interest.

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