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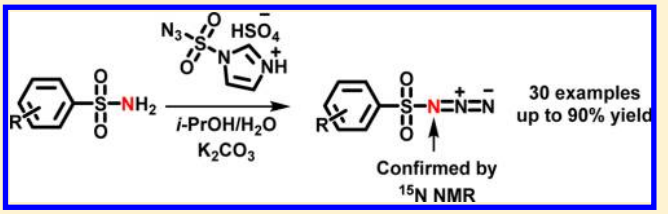
Synthesis of Sulfonyl Azides via Diazotransfer using an Imidazole-1-sulfonyl Azide Salt: Scope and ^{15}N NMR Labeling Experiments

Marc Y. Stevens, Rajiv T. Sawant, and Luke R. Odell*

Organic Pharmaceutical Chemistry, Department of Medicinal Chemistry, Uppsala Biomedical Center, Uppsala University, P.O. Box 574, SE-751 23 Uppsala, Sweden

Supporting Information

ABSTRACT: Imidazole-1-sulfonyl azide hydrogen sulfate is presented as an efficient reagent for the synthesis of sulfonyl azides from primary sulfonamides. The described method is experimentally simple and high-yielding and does not require the addition of Cu salts. Furthermore, ^{15}N NMR mechanistic studies show the reaction proceeds via a diazo transfer mechanism. Imidazole-1-sulfonyl azide hydrogen sulfate provides a considerable advantage over existing diazo transfer reagents in terms of impact stability, cost, and ease of use.



INTRODUCTION

Sulfonyl azides have gained considerable interest over the past decade as they provide a versatile starting point for the preparation of a diverse spectrum of organic compounds.[1,2] This is due to their remarkable ability to act as either three-nitrogen or one-nitrogen sources in copper-catalyzed azide−alkyne cycloaddition (CuAAC) reactions. Thus, sulfonyl azides can be selectively transformed into 1,2,3-triazoles via a standard CuAAC process[3,4] or alternatively into amidines, amidates, or amides via a cycloaddition/isomerization process to generate a highly reactive ketenimine intermediate.[1] This latter approach has recently been applied in the development of one-pot synthesis of tetrasubstituted imidazoles,[5] a phosphite-mediated synthesis of *N*-toluenesulfonylamidines,[6] and a multicomponent cascade synthesis of substituted iminocoumarins.[7] Finally, sulfonyl azides have also been employed as nitrene precursors in transition metal catalysis C−H amidations and enantioselective enzymatic C−H aminations.[8]

In the course of a parallel project, a key sulfonyl azide precursor for ^{11}C-labeling of an angiotensin II type 2 receptor (AT_2R) agonist was required.[9] Traditionally, sulfonyl azides have been prepared from the corresponding sulfonyl chloride using sodium azide in acetonitrile, but this route is hampered by the limited availability of starting materials and labile reagents.[10−13] Solvent choice is of utmost importance, as sodium azide is known to form explosive diazidomethane in the presence of polyhalomethanes, with sometimes explosive results.[12] To circumvent these issues, Fokin and co-workers devised a method using widely available sulfonamides, which are both air and moisture stable and unreactive to most functional groups.[14] This method employed trifluoromethane sulfonyl azide (**I**, Figure 1), a diazo transfer reagent which is shock-sensitive, costly, and lacking a standardized synthetic procedure, must be prepared immediately prior to use in varying yields. This was followed very recently[15] by the synthesis of *N*,*N*′-disulfonylamidines from sulfonamides and acetylenes using nonafluorobutanesulfonyl azide (**II**) as the diazo transfer reagent.[16] Although **II** is shelf-stable and cost-efficient, it is a liquid at room temperature, whereas imidazole-1-sulfonyl azide hydrogen sulfate[17] (**III**) is easily prepared from cheap starting materials in reproducible yields and is a solid at room temperature. Moreover, the integrity of **III** can readily be determined by appearance and ^1H NMR and melting point determination, whereas this is not possible with **II**. In addition, a recent study[17] investigating the explosive potential and shock sensitivity of various imidazole sulfonyl azide salts showed **III** to be largely resistant to electrostatic discharge and of low shock sensitivity (albeit not completely insensitive). At the onset of our study, no similar investigation has been carried out on **II**, leading us to select **III** for further evaluation as a diazo transfer reagent. Although **III** (as its hydrochloride salt[18]) has been employed in the functionalization of aliphatic and aromatic amines,[19−22] there is only one reported example of this class of diazo transfer reagent being used for the preparation of aryl sulfonyl azides in the literature.[14] Moreover, this example was reported without any detailed experimental information, and accordingly, we wished to expand the scope of this useful reaction.

RESULTS AND DISCUSSION

We began by identifying suitable conditions for the transformation of an aryl sulfonamide to an aryl sulfonyl azide using **III**. Although previous workers[14,23] have reported the use of a ternary solvent system, we sought to simplify the synthetic protocol by replacing it with a binary or single solvent system. This led us to choose the conditions of Stick

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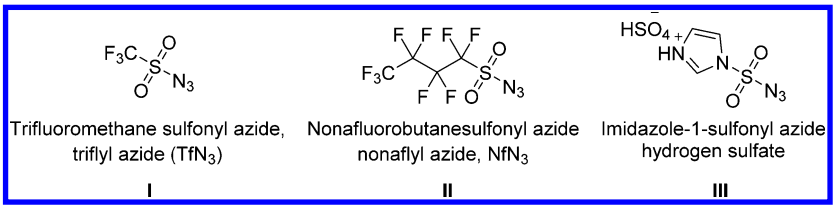
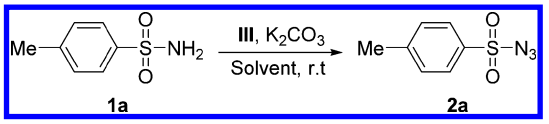


Figure 1. Diazotransfer reagents previously used for the preparation of sulfonyl azides (**I** and **II**) and employed in this work (**III**).

et al. as a starting point.[18] In a test reaction, **III** was added to a mixture of *p*-toluenesulfonamide and inorganic base (K_2CO_3) and allowed to stir for 18 h at ambient temperature (entry 1, Table 1). This initial approach did not give any detectable product by LC/MS analysis, leading us to investigate *i*-PrOH as a solvent. Once again, no product was observed, most likely due to solubility issues with the base. Gratifyingly, the addition of H_2O to the solvent system proved helpful, with a marked increase in yield (entry 3). Introduction of $CuSO_4$ did not appear to affect the outcome of the reaction (entry 4), and we therefore chose to continue our studies using metal-free conditions. Comparable yields were also achieved using both *i*-PrOH and THF in a 1:1 ratio with H_2O (entries 5 and 6). At this point, we suspected that 2 equiv of base might not be sufficient to ensure full conversion to the desired sulfonylamide anion in the presence of the diprotic salt **2**. To our delight, increasing the number of equivalents of base to 4 resulted in complete consumption of **1a**, and the product **2a** could be isolated in 86% yield (entry 7). Although switching the solvent system to *i*-PrOH/H_2O was even more beneficial (entry 8), the number of equivalents of diazo transfer reagent could not be reduced without concomitant reduction in yield (entry 9).

Table 1. Optimization of the Reaction Conditions for the Preparation of 2a from 1 Using Diazotransfer Reagent III

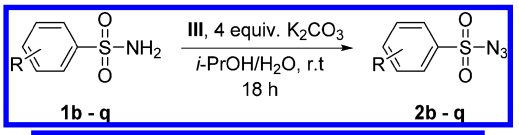


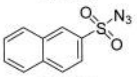
entry	base, equiv	solvent	time (h)	yield[a] (%)
1[b]	K_2CO_3, 2	MeOH	18	
2	K_2CO_3, 2	*i*-PrOH	18	
3	K_2CO_3, 2	MeOH/H_2O[c]	18	29
4[b]	K_2CO_3, 2	MeOH/H_2O[c]	18	32
5	K_2CO_3, 2	THF/H_2O[c]	18	33
6	K_2CO_3, 2	*i*-PrOH/H_2O[c]	18	45
7	K_2CO_3, 4	MeOH/H_2O[c]	18	86
8	K_2CO_3, 4	*i*-PrOH/H_2O[c]	18	90
9[d]	K_2CO_3, 4	*i*-PrOH/H_2O[c]	18	78

[a]Isolated yield. [b]5 mol % of $CuSO_4$ was added. [c]1/1 mixture. [d]1.3 equiv of diazo transfer reagent used. Typical procedure: A 2−5 mL reaction vial was charged with sulfonamide (0.5 mmol), base (1−2 mmol), and solvent (6 mL). After 5 min of stirring, the diazo transfer reagent (0.75 mmol) was added and the reaction stirred for 18 h.

Having identified suitable reaction conditions, we then sought to explore the scope and limitations of the diazo transfer reaction. As can be seen in Table 2, the reaction displayed a wide substrate scope and gave the target sulfonyl azides in good to excellent yields. Electron-rich sulfonamides (**2c−e,g,h,q**) were found to be excellent substrates with full conversion of starting material taking place in as little as 8 h (**2c**). Sulfonamides bearing various halogen substitutents such as bromide, chloride, and fluoride also performed well giving good yields of the desired products (**2b,i−k,n**). Notably, the reaction also tolerated a number of potentially reactive substituents (see **2h,o,p**), as well sterically hindered *ortho*-substituted sulfonamides (**2e,i,l**). Increasing the scale to 1 mmol had no negative impact on the isolated yield, with **2l** and **2q** giving 84 and 83%, respectively.

Table 2. Synthesis of Sulfonyl Azides 2 from Primary Sulfonamides 1 Using Optimized Conditions (Isolated Yields Shown)



entry	R	product	yield (%)
1	4-Br	**2b**	77
2	4-OMe	**2c**	80, 81[a]
3	3-Me	**2d**	63
4	2-Me	**2e**	80
5		**2f**	65[b]
6	4-*t*-Bu	**2g**	71
7	4-OH	**2h**	83
8	2-Br	**2i**	81
9	4-Cl	**2j**	74
10	3-Cl	**2k**	66
11	2-CF_3	**2l**	75, 84[d]
12	4-CF_3	**2m**	52
13	4-F	**2n**	63[c]
14	4-Ac	**2o**	76
15	4-CN	**2p**	68
16	3-OMe	**2q**	83[d]

[a]8 h reaction time. [b]66 h reaction time. [c]0.25 mmol scale. [d]1.1 mmol scale.

To further explore the scope of the reaction, we applied our modified conditions to more complex aryl and heteroaryl substrates (Table 3). Notably, the diuretics furosemide and hydrochlorothiazide were transformed into their corresponding sulfonyl azides in excellent yield, despite the presence of *ortho* substituents and acidic functionalities (**4b** and **4k**). Electron-rich and electron-poor heterocyclic substrates performed excellently (**4a**, **4c**, **4e**, **4j** and **4m**), whereas the presence of a basic nitrogen *ortho* to the sulfonyl amide was detrimental to the reaction, presumably by decreasing nucleophilicity, and full conversion of starting material was not achieved despite prolonged reaction times (**4h** and **4i**). Similarly, the antipsychotic sulpiride (**3l**) reacted sluggishly, most likely due to interaction of the basic nitrogen with **III**. Disappointingly, the reaction scope could not be extended to alkyl sulfonamides, and only trace amounts of **4f** were detected by GC/MS analysis.[24] Finally, cinnamic ester

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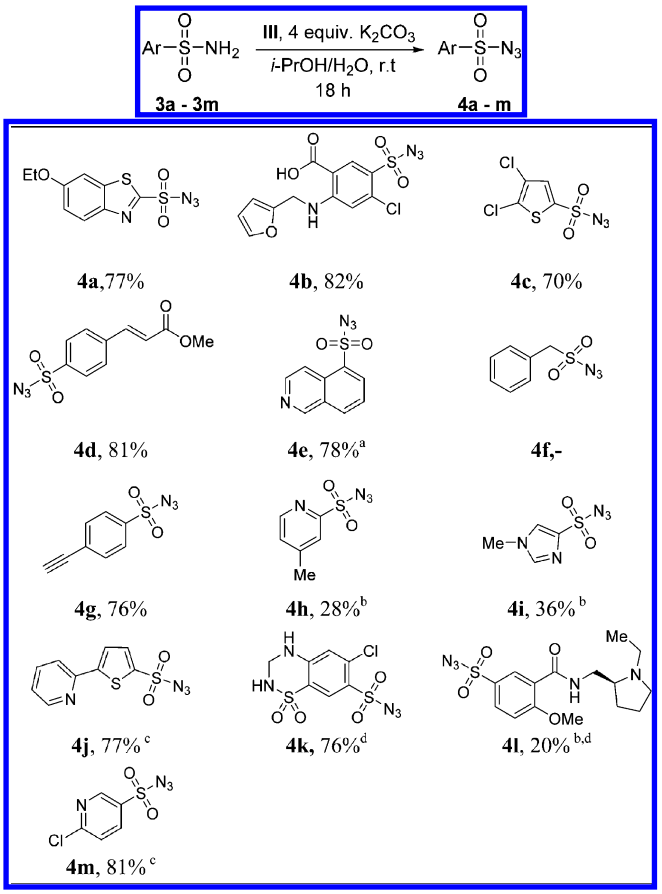
Table 3. Synthesis of Aryl and Heteroaryl Sulfonyl Azides 4 from Sulfonamides 3 (Isolated Yields Shown)



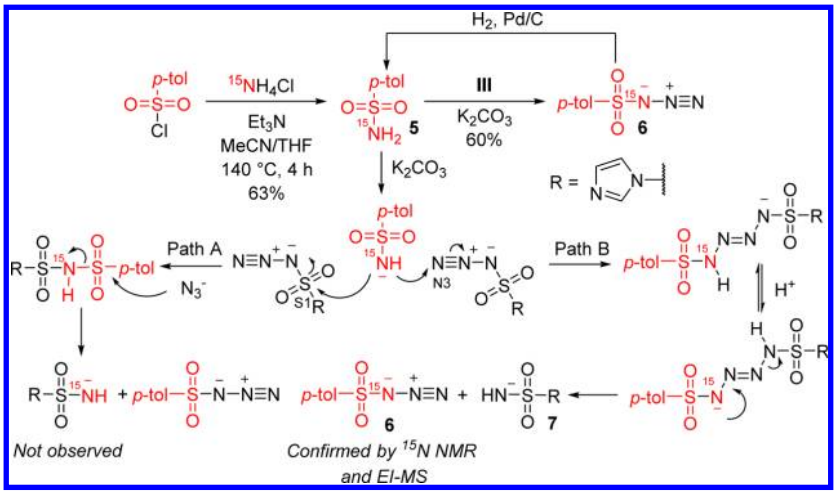
[a]0.11 mmol scale. [b]stirred for 48 h. [c]0.25 mmol scale. [d]1.00 mmol scale.

derivative **3d** and alkyne **3g** were smoothly transformed into **4d** and **4g** under our metal-free reaction conditions, with no traces of cycloaddition-derived byproducts being observed by LC/MS analysis.

Two plausible mechanistic pathways for our reaction are presented in Scheme 1. The first step is believed to be generation of the nucleophilic sulfonamide anion. Conducting the reaction in the absence of base or in the presence of a weaker base (sodium acetate) gave only traces of the desired product. Once generated, the nucleophile can attack either the electrophilic sulfur center S1 or the terminal azide nitrogen of **III**. Attack on sulfur (Scheme 1, path A) will expel an azide anion, which can then displace the tosylamide group to give the sulfonyl azide product. In path B, the nucleophile attacks at the azide nitrogen generating a tetrazine intermediate, which then collapses to give the sulfonyl azide product. In the reaction of primary amines with *p*-toluenesulfonyl azide and other diazo transfer reagents, the reaction is believed to proceed via a diazo transfer pathway (path B), as evidenced by the retention of configuration when using chiral amines.[25] In contrast, the reaction mechanism for the synthesis of sulfonyl azides from sulfonyl amides has not yet been explored. Moreover, the achiral nature of the sulfonamide group does not allow path A to be ruled out based on retention or inversion of configuration. Accordingly we decided to investigate the mechanism for the reaction using ^{15}N isotopic labeling. To this end, we first prepared ^{15}N labeled tosyl amide **5** and subjected it to our standard conditions. This resulted in the exclusive formation of a product with m/z of +1, confirmed as the hitherto unreported *p*-toluene sulfonyl azide-1-^{15}N (**6**). These findings were in line with previous work,[26] confirming that diazo transfer (see Scheme 1, path B), and not azidation (via attack on S1 of **C**) had taken place. The efficiency of **III** as a diazo transfer reagent may be, in part, due to the greater leaving group ability of the electron-poor imidazole group.[27] Furthermore, imidazole-1-sulfonamide was not observed in any crude reaction mixtures (LC/MS analysis) suggesting that it may be hydrolytically labile under the basic conditions, thus preventing diazo transfer from **6** to **7**.

In order to determine the position of the label, we then proceeded to reduce the product to the corresponding sulfonamide, and NMR and ESI/MS analysis of all three steps confirmed full conversion of the azide to the original sulfonamide with no loss or scrambling of the ^{15}N label, thus confirming the position of the ^{15}N label at N1 of the sulfonyl azide. To the best of our knowledge, this is the first reported synthesis of *p*-toluene sulfonyl azide-1-^{15}N and this compound should be useful for probing the mechanism of other sulfonyl azide reactions as well as in the production of other ^{15}N-labeled compounds.

Scheme 1. Proposed Reaction Pathway Based on ^{15}N-Labeling Studies



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CONCLUSIONS

In summary, we have expanded the scope of the diazo transfer reaction using the stable and easy-to-handle imidazole-sulfonyl azide salt **III**. The reaction was found to tolerate a wide range of functional groups and afforded good to excellent yields of the sulfonyl azide products without the addition of Cu salts. Furthermore, the reaction was exemplified by the synthesis of N1-labeled ^{15}N labeled tosyl azide, and this compound was used to elucidate the reaction mechanism. The reaction was shown to proceed via a diazo transfer process following nucleophilic attack at the terminal azide nitrogen in **III**. Work is currently underway in our laboratory on extending this reaction to alkyl sulfonamides.

EXPERIMENTAL SECTION

General Information. Analytical thin-layer chromatography was performed on silica gel 60 F-254 plates and visualized with UV light. Flash column chromatography was performed on a silica gel 60 (40−63 μm) and visualized with UV light. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz respectively using $CDCl_3$, MeOD, CD_3CN or DMSO-d_6 as a solvent. ^{15}N NMR spectra were recorded at 40 MHz. Chemical shifts are referenced to TMS or HNO_3 via residual solvent signals. All reactions were performed in loosely capped reaction vials designed for 2−6 mL reaction volumes, with the exception of **4a**−**e**, which were carried out in loosely capped 25 mL round-bottomed flasks. Compound **5** was prepared in an Initiator single mode reactor producing controlled irradiation at 2450 MHz, and the temperature was monitored using the built-in online IR sensor. LC/MS was performed on an instrument equipped with a C18 column (50 × 3.0 mm, particle size 2.6 μm, pore size 100 Å). Accurate mass values were determined on a mass spectrometer equipped with an electrospray or electron-impact ion source and 7-T hybrid ion trap (LTQ) or TOF detector, respectively. Flash column chromatography was performed on silica gel 60 (40−63 μm). All starting materials and reagents are commercially available and were used as received, with the exception of isoquinoline-5-sulfonamide (**3e**) and methyl (*E*)-3-(4-sulfamoylphenyl)acrylate (**3d**), the syntheses of which are detailed in the Experimental Section of the paper. Imidazole-1-azide hydrogen sulfate (**III**) was prepared by the literature procedure, and spectral data for the isolated product were in agreement with literature values.[17]

Caution! Sulfonyl azides are potentially explosive, and all reactions should be carried out behind a blast shield. The authors recommend the use of plastic spatulas for handling of solid material. Mother liquors arising from the preparation of imidazole-1-sulfonyl azide should be treated with excess sodium nitrite and thereafter 20% H_2SO_4 to destroy azide species. Used silica gel should be treated in a similar fashion to destroy residues of imidazole-1-sulfonyl azide. Imidazole-1-sulfonyl azide (prepared by the literature procedure[18,28]) is highly impact-sensitive and should be handled with great care.

General Procedure 1 for Preparation of Sulfonyl Azides 2a−p and 4f−m Exemplified by 4-*tert*-Butylbenzenesulfonyl Azide (2g). To a vigorously stirred solution of sulfonamide (106 mg, 0.5 mmol) and K_2CO_3 (276 mg, 2 mmol) in 6 mL of solvent (1:1 H_2O/*i*-PrOH) in a reaction vial was added diazo transfer reagent **III** (203 mg, 0.75 mmol). After being stirred for 18 h at ambient temperature, the reaction mixture was diluted with 20 mL saturated $NaHCO_3$ and extracted with 2 × 50 mL EtOAc. The combined organic phases were washed twice with brine and dried over Na_2SO_4 and the volatiles evaporated in vacuo. The residue was purified by silica gel chromatography (10% EtOAc in *n*-pentane unless otherwise stated) to afford the title compound azide as a white solid (84 mg, 71%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 8.5 Hz, 2H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 135.5, 127.4, 126.7, 35.5, 31.0; IR (neat) cm^{-1} 2127; MS (EI) calcd for $C_{10}H_{13}N_3O_2S$ m/z 239.0728, found m/z 239.0737.

*4-Methylbenzenesulfonyl azide (**2a**):*[29] colorless liquid (88 mg, 90%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 135.7, 130.6, 130.5, 127.7, 127.7, 22.0; IR (neat) cm^{-1} 2126; MS (EI) m/z 197.1.

*4-Bromobenzesulfonyl azide (**2b**):*[14] white solid (101 mg, 77%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.8 Hz, 2H), 7.76 (dd, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 133.0, 130.3, 128.9; IR (neat) cm^{-1} 2126; MS (EI) m/z 260.9.

*4-Methoxybenzenesulfonyl azide (**2c**):*[14] white solid (104 mg, 80%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.95−7.79 (m, 2H), 7.15−6.92 (m, 2H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 130.2, 130.1, 115.2, 56.2; IR (neat) cm^{-1} 2126; MS (EI) m/z 213.1.

*3-Methylbenzenesulfonyl azide (**2d**):*[30] colorless liquid (62 mg, 63%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.85−7.64 (m, 2H), 7.58−7.41 (m, 2H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 138.6, 135.9, 129.8, 128.0, 124.9, 21.7; IR (neat) cm^{-1} 2125; MS (EI) m/z 197.0.

*2-Methylbenzenesulfonyl azide (**2e**):*[31] colorless liquid (79 mg, 80%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.21−7.94 (m, 1H), 7.58 (td, J = 7.6, 1.5 Hz, 1H), 7.41 (d, J = 7.6 Hz, 2H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 136.8, 134.7, 133.1, 129.4, 126.5, 20.4; IR (neat) cm^1 2123; MS (EI) m/z 197.1.

*2-Naphthylbenzenesulfonyl azide (**2f**):*[14] stirred for 66 h; white solid (75 mg, 65%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.03 (dd, J = 11.1, 8.4 Hz, 2H), 7.96 (d, J = 8.1 Hz, 1H), 7.89 (dd, J = 8.7, 2.0 Hz, 1H), 7.77−7.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 135.5, 132.2, 130.5, 130.3, 129.9, 129.9, 129.8, 128.5, 128.4, 122.1; IR (neat) cm^{-1} 2119; MS (EI) m/z 233.9.

*4-Hydroxybenzenesulfonyl azide (**2h**):*[14] colorless liquid (82 mg, 83%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.03−7.54 (m, 2H), 7.14−6.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 130.5, 130.5, 129.6, 116.8; IR (neat) cm^{-1} 2124; MS (EI) m/z 199.01.

*2-Bromobenzenesulfonyl azide (**2i**):*[14] colorless liquid (106 mg, 81%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.34−8.08 (m, 1H), 7.92−7.71 (m, 1H), 7.60−7.47 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 136.1, 135.7, 132.1, 128.2, 121.0; IR (neat) cm^{-1} 2132; MS (EI) m/z 262.9.

*4-Chlorobenzenesulfonyl azide (**2j**):*[29] colorless liquid (80 mg, 74%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 136.8, 130.0, 128.9; IR (neat) cm^{-1} 2129; MS (EI) m/z 217.0

*3-Chlorobenzenesulfonyl azide (**2k**):*[32] colorless liquid (72 mg, 66%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (t, J = 1.9 Hz, 1H), 7.90−7.78 (m, 1H), 7.76−7.63 (m, 1H), 7.57 (t, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 136.1, 135.1, 131.1, 127.6, 125.7; IR (neat) cm^{-1} 2127; MS (EI) m/z 217.1.

*2-(Trifluoromethyl)benzenesulfonyl azide (**2l**):*[33] white solid (95 mg, 75%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, J = 7.5, 1.9 Hz, 1H), 7.97 (dd, J = 7.5, 1.7 Hz, 1H), 7.91−7.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 134.8, 132.8, 132.1, 128.8 (q, $^3J_{CF}$ = 6.1 Hz), 128.3, 123.3 (q, $^4J_{CF}$ = 274.0 Hz); IR (neat) cm^{-1} 2133; MS (EI) m/z 251.1.

*4-(Trifluoromethyl)benzenesulfonyl azide (**2m**):*[34] white solid, eluting in 6% EtOAc in pentane (65 mg, 52%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.2 Hz, 2H), 7.90 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8 (q, $^3J_{CF}$ = 1.4 Hz), 136.3 (q, $^2J_{CF}$ = 33.4 Hz), 128.1, 126.89 (q, $^3J_{CF}$ = 3.7 Hz), 121.5 ppm (q, $^4J_{CF}$ = 273.4 Hz); IR (neat) cm^{-1} 2131; MS (EI) m/z 251.1.

*4-Fluorobenzenesulfonyl azide (**2n**):*[34] colorless liquid (32 mg, 63%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.27−7.69 (m, 2H), 7.39−6.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7 (d, $^1J_{CF}$ = 258.7 Hz), 134.9 (d, $^4J_{CF}$ = 3.7 Hz), 130.5 (d, $^3J_{CF}$ = 9.9 Hz), 117.1 (d, $^2J_{CF}$ = 23.0 Hz); IR (neat) cm^{-1} 2128; MS (EI) m/z 201.1.

*4-Acetylbenzenesulfonyl azide (**2o**):*[35] colorless solid (85 mg, 76%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.6 Hz, 2H), 8.04 (d, J = 8.6 Hz, 2H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 141.9, 141.6, 129.4, 127.8, 26.9; IR (neat) cm^{-1} 2140; MS (EI) m/z 225.1.

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*4-Cyanobenzenesulfonyl azide (**2p**):*[36] white solid (71 mg, 68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 133.8, 128.4, 118.8, 117.0; IR (neat) cm^{-1} 2129; MS (EI) m/z 208.0.

*3-Methoxybenzenesulfonyl azide (**2q**):*[37] colorless liquid (185 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.44 (m, 2H), 7.45−7.36 (m, 1H), 7.32−7.12 (m, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 139.6, 121.6, 119.8, 112.2, 56.1; IR (neat) cm^{-1} 2128; MS (EI) m/z 213.1.

*Methyl (E)-3-(4-Sulfamoylphenyl)acrylate (**3d**).* To a stirred mixture of methyl (*E*)-3-(4-(*N*-(*tert*-butyl)sulfamoyl)phenyl)acrylate (72 mg, 0.24 mmol) in anhydrous DCM (20 mL) at 0 °C under N_2 atmosphere was added BCl_3 (1 M, 2.66 mL, 2.66 mmol). The reaction mixture was stirred for 1 h at ambient temperature and monitored by TLC (25% EtOAc in *n*-pentane). Upon completion, the reaction mixture was coevaporated with 3 × 10 mL $CHCl_3$ and the residue purified by silica gel chromatography (20−40% EtOAc in *n*-pentane) to provide the title compound as a white solid (32 mg, 55%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.3 Hz, 2H), 7.75 (d, J = 16.1 Hz, 1H), 7.48 (s, 2H), 6.82 (dd, J = 16.1, 0.7 Hz, 1H), 3.78 (d, J = 0.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.3, 146.1, 143.7, 138.1, 129.7, 127.0, 121.3, 52.6; HRMS calcd for $C_{10}H_{10}NO_4S$ [M $^-$] m/z 240.0331, found m/z 240.0324.

*Isoquinoline-5-sulfonamide (**3e**).*[38] Isoquinoline-5-sulfonic acid (2 g, 9.27 mmol) was dissolved in 40 mL of $SOCl_2$ and refluxed for 8 h. The resulting slurry was suspended in 20 mL of dichloromethane, and 20 mL of NH_4OH was added at 0 °C. After the mixture was stirred for 18 h, the pH was adjusted to 7 by the addition of 1 M HCl and the aqueous phase extracted with 2 × 100 mL EtOAc. The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo, providing the title compound as a yellow solid (208 mg, 10%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.45 (s, 1H), 8.67 (d, J = 6.0 Hz, 1H), 8.51−8.24 (m, 3H), 7.83−7.78 (m, 1H), 7.77 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) 153.5, 144.5, 138.6, 132.9, 130.7, 130.4, 128.8, 126.6, 117.7; ESI (MS) m/z 208.78.

General Procedure II for Compounds 4a−e. As for compounds **2a−q** but with 12 mL of solvent.

*6-Ethoxybenzo[d]thiazole-2-sulfonyl azide (**4a**):* white solid (160 mg, 77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 9.1 Hz, 1H), 7.36 (d, J = 2.5 Hz, 1H), 7.29−7.21 (m, 1H), 4.14 (q, J = 7.0 Hz, 2H), 1.49 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 159.0, 146.4, 138.9, 126.5, 119.2, 103.8, 64.4, 14.6; IR (neat) cm^{-1} 2146; MS (ESI) calcd for $C_9H_9N_4O_3S_2$ m/z 285.0116 ([M + H$^+$]), found m/z 285.0118.

*5-(Azidosulfonyl)-4-chloro-2-((furan-2-ylmethyl)amino)benzoic acid (**4b**):* tan solid, eluting in 20−80% EtOAc in hexanes (157 mg, 82%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39−8.94 (m, 1H), 8.41 (s, 1H), 7.61 (dd, J = 1.9, 0.9 Hz, 1H), 7.22 (s, 1H), 6.54−6.15 (m, 2H), 4.63 (d, J = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.1, 155.1, 151.8, 143.8, 136.9, 136.7, 120.2, 115.2, 111.5, 108.8, 40.1; IR (neat) cm^{-1} 2130; MS (ESI) calcd for $C_{12}H_9ClN_4O_5S$ m/z 357.0060 ([M + H$^+$]), found m/z 357.0061.

*4,5-Dichlorothiophene-2-sulfonyl azide (**4c**):* white solid (90 mg, 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ135.9, 135.0, 133.6, 126.0; IR (neat) cm^{-1} 2131; MS (EI) calcd for $C_4HCl_2N_3O_2S_2$ m/z 256.8887 ([M + H$^+$], found m/z 256.8893.

*Methyl (E)-3-(4-(azidosulfonyl)phenyl)acrylate (**4d**):* white solid, eluting in 20% EtOAc in hexanes (85 mg, 81%); ^{1}H NMR (400 MHz, $CDCl_3$) 7.96 (d, J = 8.4 Hz, 2H), 7.86−7.58 (m, 3H), 6.57 (d, J = 16.1 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 166.7, 142.1, 141.0, 139.5, 129.2, 128.4, 122.7, 52.4; IR (neat) cm^{-1} 2129; MS (ESI) calcd for $C_{10}H_{10}N_3O_4S$ m/z 268.0392 ([M + H$^+$]), found m/z 268.0389.

*Isoquinoline 5-sulfonyl azide (**4e**):*[39] colorless liquid, eluting in 50% EtOAc in hexanes (21 mg, 78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.77 (d, J = 6.0 Hz, 1H), 8.52 (dd, J = 7.4, 1.2 Hz, 1H), 8.32 (dd, J = 12.4, 7.2 Hz, 2H), 7.77 (t, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 146.4, 136.0, 134.0, 133.4, 131.5, 129.3, 126.1, 117.3; IR (neat) cm^{-1} 2136; MS (ESI) calcd for $C_9H_7N_4O_2S$ m/z 235.0290 ([M + H$^+$]), found m/z 235.0283.

*4-Ethynylbenzenesulfonamide (**4g**):* white solid, eluting in 50% EtOAc in hexanes (103 mg, 76%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04−7.78 (m, 2H), 7.69 (d, J = 8.5 Hz, 2H), 3.35 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 133.5, 130.4, 129.2, 82.6, 81.8; IR (neat) cm^{-1} 2131; MS (EI) calcd for $C_8H_5N_3O_2S$ m/z 207.0108, found m/z 207.0102.

*4-Methylpyridine-2-sulfonyl azide (**4h**):*[30] stirred for 48 h; colorless liquid, eluting in 20% EtOAc in hexanes (30 mg, 28%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (d, J = 2.2 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.85−7.72 (m, 1H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 151.4, 139.7, 138.8, 122.1, 19.1; IR (neat) cm^{-1} 2132; MS (ESI) m/z 198.91.

*1-Methylimidazole-4-sulfonyl azide (**4i**):*[40] stirred for 48 h; white solid (17 mg, 36%); ^{1}H NMR (400 MHz, $CDCl_3$) δ δ 7.61 (s, 1H), 7.57 (s, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 139.3, 125.8, 34.6; IR (neat) cm^{-1} 2133; MS (ESI) m/z 187.92.

*5-(Pyridin-2-yl)thiophene-2-sulfonyl azide (**4j**):* white solid, eluting in 50% EtOAc in hexanes (66 mg, 77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70−8.48 (m, 1H), 7.83−7.76 (m, 2H), 7.72 (d, J = 7.7 Hz, 1H), 7.56 (d, J = 4.1 Hz, 1H), 7.36−7.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 150.6, 150.4, 138.7, 137.5, 135.7, 124.5, 124.0, 119.7; IR (neat) cm^{-1} 2135; MS (ESI) calcd for $C_9H_7N_4O_2S_2$ ([M + H$^+$]) m/z 267.0010, found m/z 267.0007.

*6-Chloro-3,4-dihydro-2H-benzo[e][1,2,4]thiadiazine-7-sulfonyl azide 1,1-dioxide (**4k**):* white solid, eluting in 50% EtOAc in hexanes (245 mg, 76%); ^{1}H NMR (400 MHz, methanol-d_4) δ 8.19 (s, 1H), 7.06 (s, 1H), 4.86 (s, 2H); ^{13}C NMR (100 MHz, methanol-d_4) δ 148.7, 135.7, 128.8, 122.1, 119.3, 117.6, 54.6; IR (neat) cm^{-1} 2237; MS (ESI) calcd for $C_7H_7ClN_5O_4S_2$ m/z 323.9628, found m/z 323.9624.

*(S)-3-(((1-Ethylpyrrolidin-2-yl)methyl)carbamoyl)-4-methoxybenzenesulfonyl azide (**4l**):* stirred for 48 h; colorless solid, eluting in 7% MeOH in dichloromethane (72 mg, 20%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, J = 2.6 Hz, 1H), 8.29 (s, 1H), 8.01 (dd, J = 8.8, 2.6 Hz, 1H), 7.15 (d, J = 8.9 Hz, 1H), 4.07 (s, 3H), 3.74 (ddd, J = 13.9, 7.2, 3.0 Hz, 1H), 3.36 (dt, J = 14.0, 3.8 Hz, 1H), 3.31−3.18 (m, 1H), 2.93−2.80 (m, 1H), 2.74 (s, 1H), 2.35−2.21 (m, 2H), 1.92 (dt, J = 12.2, 8.2 Hz, 1H), 1.83−1.55 (m, 3H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ163.1, 161.8, 132.3, 131.9, 131.0, 123.5, 112.3, 62.3, 56.6, 53.7, 48.1, 41.3, 28.4, 23.0, 14.0; IR (neat) cm^{-1} 2130; MS (ESI) calcd for $C_{15}H_{22}N_5O_4S$ ([M + H$^+$]) m/z 368.1393, found m/z 368.1392.

*6-Chloropyridine-3-sulfonyl azide (**4m**):* white solid, eluting in 50% EtOAc in hexanes (42 mg, 81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.79 (d, J = 5.3 Hz, 1H), 7.59 (d, J = 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 151.5, 143.5, 133.9, 126.8; IR (neat) cm^{-1} 2143; MS (ESI) calcd for $C_5H_4ClN_4O_2S$ ([M + H$^+$]) m/z 218.9744, found m/z 218.9746.

***p*-Toluenebenzenesulfonamide-^{15}N (5).**[41] To a stirred solution of *p*-toluenesulfonyl chloride (325 mg, 1.7 mmol) in 5 mL of a 3:2 mixture of MeCN/THF were added $^{15}NH_4Cl$ (98 atom % ^{15}N, 102 mg, 1.8 mmol) and Et_3N (1178 μL, 8.5 mmol), and the mixture was heated under microwave irradiation at 140 °C for 4 h. After being cooled to room temperature, the volatiles were evaporated and the residue taken up in satd $NaHCO_3$ and extracted with 2 × 20 mL EtOAc. The combined organic phases were dried over Na_2SO_4, concentrated, and purified by silica gel chromatography (30% EtOAc in hexanes), providing the title compound as a tan solid (186 mg, 63%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88−7.65 (m, 2H), 7.60−7.31 (m, 3H), 7.21 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) 141.4, 141.4, 129.3, 125.4, 20.9; ^{15}N NMR (40 MHz, $CDCl_3$) −284.9; ^{15}N/^{14}N 98.9/1.1% as determined by MS (EI).

***p*-Toluenesulfonyl Azide-(^{15}N)-1 (6).** Prepared from **5** following general procedure **I**: colorless liquid (60 mg, 60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 135.5, 135.5, 130.2, 127.5, 127.5, 21.7; ^{15}N NMR (40 MHz. $CDCl_3$) −280.2; IR

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(neat) cm^{-1} 2122; MS (EI) calcd for $C_7H_7N_2{}^{15}NO_2S$ m/z 198.0229, found 198.0228.

Reduction of 6. To a methanolic solution of **6** (38 mg, 0.19 mmol) in a 2−5 mL reaction vial was added Pd/C (10% Pd, 3 mg, 0.03 mmol) and the mixture stirred under H_2 atmosphere at ambient temperature for 30 min. After filtration, the reaction mixture was concentrated in vacuo and the crude material analyzed without further purification. $^{15}N/^{14}N$ 98.6/1.4% as determined by MS (ESI).

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C spectra for all products and ^{15}N spectra for **5** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +46-18-4714297. Fax: +46-18-4714474. E-mail: luke.odell@orgfarm.uu.se.

Notes

The authors declare no competing financial interest.

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