Synthesis of Sulfonyl Azides

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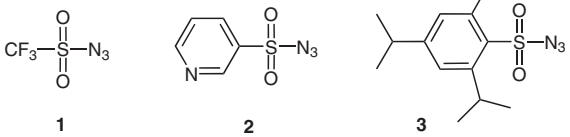
Abstract: 1-(Alkylsulfonyl)- and 1-(arylsulfonyl)benzotriazoles react with sodium azide in acetonitrile to give the corresponding alkanesulfonyl and arenesulfonyl azides.

Key words: synthesis, 1-sulfonylbenzotriazoles, sulfonyl azides, sodium azide, Grignard reagent

Sulfonyl azides (RSO_2N_3) are valuable reagents for diazo transfer to the α-methylene position of carbonyl compounds such as β-oxo esters and oxo sulfones.[1,2] Charette and co-workers reported trifluoromethanesulfonyl azide (triflyl azide, **1**), a highly electrophilic diazo-transfer reagent, gives good results with activated acetic acid esters and ketones (Figure 1).[3,4] 3-Pyridinesulfonyl azide (**2**) appears to be more efficient for radical azidating than 4-(methoxycarbonyl)benzenesulfonyl azide and 3- and 4-carboxybenzenesulfonyl azides.[5,6] Sulfonyl azides [especially 2,4,6-triisopropylbenzenesulfonyl azide (**3**)] have been used in the α-azidation of amide enolates and ester enolates in the synthesis of α-amino acid derivatives.[7]

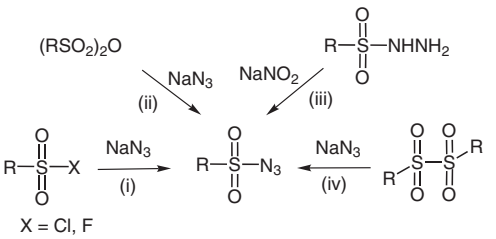


1 **2** **3**

Figure 1

The reaction of sodium azide with a sulfonyl halide is the most direct synthetic approach to sulfonyl azides (Scheme 1).[6,8–10] Less common approaches include reactions of sulfonyl anhydrides and α-disulfones with sodium azide.[11–13] Diazotization of sulfonyl hydrazides with NO^+ has also been employed but requires the availability of the hydrazides.[14,15] All these procedures may suffer from the unavailability of starting materials or their difficulty in preparation, thus a new and convenient method for the preparation of sulfonyl azides would be advantageous.

Recently, we developed a general and facile method for the preparation of 1-sulfonylbenzotriazoles **4** as a practical alternative to the frequently labile and often difficult to access sulfonyl halides.[16] 1-Sulfonylbenzotriazoles **4** provide efficient N-sulfonylation of amines and C-sulfonylation of nitriles, heteroaromatics, sulfones and esters to produce α-cyanoalkyl sulfones, sulfonylheteroaromatics, α-sulfonylalkyl sulfones and esters of α-sulfonyl acids, respectively.[17] They are also useful in the synthesis of *N*-acylbenzotriazole from the corresponding carboxylic acid.[18–20] Herein we report the application of 1-sulfonylbenzotriazoles to the preparation of sulfonyl azides.



Scheme 1 Survey of various syntheses of sulfonyl azides

1-Sulfonylbenzotriazoles **4** are accessible from aryl- and alkyllithium or Grignard reagents by reaction with sulfur dioxide and 1-chlorobenzotriazole (Table 1).[16]

Treatment of **4** with sodium azide (1.5 equiv) in acetonitrile for 3–10 hours under reflux gave the sulfonyl azides **5** in synthetically useful yields (Table 2). This approach affords a variety of novel alkanesulfonyl and heteroarenesulfonyl azides (compounds **5b**, **5e**, **5f**, **5h**, **5i** and **5k–n**) and improved the yields for compounds **5a** and **5g** (the yield for compound **5a** is not reported in the literature). An advantage of our procedure is the use of 1-sulfonylbenzotriazoles which are crystalline compounds, easily accessible, and stable to storage over years. Furthermore, this approach avoids the use of hydrazides and NO^+ equivalents, and multistep syntheses.

The present procedure requires only simple manipulations and low-priced reagents; thus, it should be appropriate for providing highly demanded derivatives. The present work provides additional evidence for the good leaving ability of a benzotriazole group.

In conclusion, a new method for the synthesis of a variety of alkanesulfonyl, arenesulfonyl and heteroarenesulfonyl azides has been developed using 1-sulfonylbenzotriazoles. This approach broadens the range of available sulfonyl azides, which are compounds of major synthetic importance.

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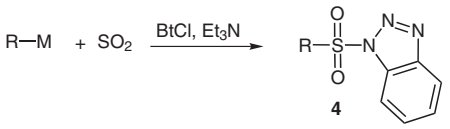
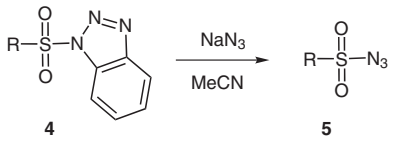
Table 1 Preparation of 1-(Alkylsulfonyl)- and 1-(Arylsulfonyl)benzotriazoles **4**



4	R	M	Yield[a] (%)	Mp (°C)	Lit. mp (°C)	Ref.
a	*n*-butyl	Li	68	oil	oil	16
b	cyclohexyl	MgCl	74	118–119	117–119	16
c	4-tolyl	MgBr	90	131–132	133–134	16
d	2-thienyl	Li	80	142–144	143–144	16
e	1-methyl-1*H*-indol-2-yl	Li	22	131–133	131–132	16
f	2-furyl	Li	85	108–109	107–109	16
g	2-pyridyl	Li	73	130–132	132–135	16
h	1-methyl-1*H*-imidazol-2-yl	Li	82	146–149	147–150	16
i	2-benzofuryl	Li	75	147–148	147–148	17
j	3-pyridyl	Li	50	128–130	128–129	16
k	5-ethyl-2-furyl	Li	60	96–97	147–148	17
l	2-thiazolyl	Li	11	114–116	–[b]	–
m	5-methyl-2-thienyl	Li	45	104–106	–[b]	–
n	5-methyl-2-furyl	Li	35	114–116	–[b]	–

[a] Isolated yields.
[b] Novel compound.

Table 2 Preparation of Alkanesulfonyl and Arenesulfonyl Azides **5**



		This work			Literature			
5	R	Time (h)	Yield[a] (%)	Mp (°C)	Method[b]	Yield (%)	Mp (°C)	Ref.
a	*n*-butyl	3	86	oil	(i)	–[c]	oil	21
b	cyclohexyl	6	55	oil	–	–	–[d]	–
c	4-tolyl	4	88	oil	(iii)	96	22–25	14
d	2-thienyl	4	70	30–32	(i)	85	31–33	22
e	1-methyl-1*H*-indol-2-yl	6	30	oil	–	–	–[d]	–
f	2-furyl	6	68	oil	–	–	–[d]	–
g	2-pyridyl	3	90	oil	(i)	66	–	23
h	1-methyl-1*H*-imidazol-2-yl	7	45	39–41	–	–	–[d]	–
i	2-benzofuryl	7	23	58–60	–	–	–[d]	–
j	3-pyridyl	6	45	oil	(i)	80	oil	24
k	5-ethyl-2-furyl	10	40	oil	–	–	–[d]	–
l	2-thiazolyl	8	25	oil	–	–	–[d]	–
m	5-methyl-2-thienyl	10	30	oil	–	–	–[d]	–
n	5-methyl-2-furyl	10	40	oil	–	–	–[d]	–

[a] Isolated yields.
[b] See Scheme 1.
[c] Yield not reported.
[d] Novel compound.

Melting points are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian 300 MHz spectrometer in $CDCl_3$ solution with TMS as internal standard. THF was distilled from sodium benzophenone ketyl prior to use. All reactions were performed under a nitrogen atmosphere and in oven-dried glassware. Column chromatography was performed on silica gel, 200–425 mesh. HRMS were recorded with a Thermoscientific DSQ mass spectrometer in CI mode.

1-Sulfonylbenzotriazoles **4a**–**k** were prepared according to previously published procedures.[16,17]

1-Sulfonylbenzotriazoles 4l–n; General Procedure

SO_2 was bubbled into a soln of an organometallic reagent (14 mmol) in anhyd THF (50 mL) at –78 °C under N_2 atmosphere until a sample of the soln no longer gave a basic pH test. 1-Chlorobenzotriazole (2.14 g, 14 mmol) was added in one portion at r.t., and the mixture was stirred for 2 h. Et_3N (1.84 mL, 14 mmol) was added, followed by stirring at r.t. for 16 h. H_2O (ca. 150 mL) was added to the reaction mixture and the product was extracted with EtOAc (3×100 mL). The combined organic layers were washed with H_2O (2×50 mL) and brine (2×50 mL), then dried ($MgSO_4$) and filtered. After concentration, the residue was purified either by recrystallization or by column chromatography over silica gel (200–425 mesh).

1-(2-Thiazolylsulfonyl)-1*H*-1,2,3-benzotriazole (4l)

White solid; yield: 11%; mp 114–116 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (t, *J* = 7.5 Hz, 1 H), 7.74 (t, *J* = 7.5 Hz, 1 H), 7.82 (d, *J* = 2.9 Hz, 1 H), 7.96 (d, *J* = 2.9 Hz, 1 H), 8.13 (d, *J* = 8.2 Hz, 1 H), 8.20 (d, *J* = 8.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 103.3, 112.5, 120.7, 126.4, 128.0, 130.9, 131.9, 145.6.

Anal. Calcd for $C_9H_6N_4O_2S_2$: C, 40.59; H, 2.27; N, 21.04. Found: C, 40.92; H, 2.08; N, 20.77.

1-(5-Methyl-2-thienylsulfonyl)-1*H*-1,2,3-benzotriazole (4m)

White solid; yield: 45%; mp 104–106 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.50 (s, 3 H), 6.79 (d, *J* = 3.2 Hz, 1 H), 7.50 (t, *J* = 8.1 Hz, 1 H), 7.68 (t, *J* = 8.0 Hz, 1 H), 7.77 (d, *J* = 3.8 Hz, 1 H), 8.06–8.13 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.8, 112.0, 120.5, 125.9, 126.8, 130.2, 131.2, 132.8, 136.4, 145.4, 152.9.

Anal. Calcd for $C_{11}H_9N_3O_2S_2$: C, 47.30; H, 3.25; N, 15.04. Found: C, 47.67; H, 3.16; N, 14.87.

1-(5-Methyl-2-furanylsulfonyl)-1*H*-1,2,3-benzotriazole (4n)

White solid; yield: 35%; mp 114–116 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 6.21 (d, *J* = 3.4 Hz, 1 H), 7.42 (d, *J* = 3.5 Hz, 1 H), 7.52 (t, *J* = 7.9 Hz, 1 H), 7.69 (t, *J* = 7.8 Hz, 1 H), 8.08 (d, *J* = 8.4 Hz, 1 H), 8.13 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 109.0, 112.1, 120.5, 123.0, 125.9, 130.3, 131.5, 142.5, 145.4, 160.9.

Anal. Calcd for $C_{11}H_9N_3O_3S$: C, 50.18; H, 3.45; N, 15.96. Found: C, 50.29; H, 3.39; N, 15.85.

Sulfonyl Azides 5a–n; General Procedure

Warning: Due to the explosive character of sulfonyl azides, all work should be performed in a fume hood, and drying of these compounds should be performed at room temperature.

NaN_3 (97 mg, 1.5 mmol) was added to a soln of a 1-sulfonylbenzotriazole **4a**–**n** (1 mmol) in MeCN (10 mL). One drop of H_2O was added and the mixture was heated under reflux for the time indicated in Table 2. The solvent was evaporated and the residue was dissolved in Et_2O (100 mL), then washed with dilute aq Na_2CO_3 (2×50 mL) and H_2O (2×50 mL). The organic layer was dried ($MgSO_4$) and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (hexane–Et_2O, 2:1) to give the sulfonyl azide.

1-Butanesulfonyl Azide (5a)[21]

Pale yellow oil; yield: 86%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.3 Hz, 3 H), 1.45–1.55 (m, 2 H), 1.85–1.97 (m, 2 H), 3.28–3.36 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.4, 21.2, 25.2, 55.7.

Cyclohexanesulfonyl Azide (5b)

Colorless oil; yield: 55%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19–1.43 (m, 3 H), 1.52–1.86 (m, 3 H), 1.87–2.01 (m, 2 H), 2.21–2.39 (m, 2 H), 3.16–3.28 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.7, 24.9, 26.2, 65.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_6H_{12}N_3O_2S$: 190.0645; found: 190.0661.

4-Toluenesulfonyl Azide (5c)[14]

Colorless oil; yield: 88%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.49 (s, 3 H), 7.41 (d, *J* = 8.1 Hz, 2 H), 7.85 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 127.5, 130.3, 135.4, 146.2.

2-Thiophenesulfonyl Azide (5d)

Pale yellow microcrystals; yield: 70%; mp 30–32 °C (Lit.[22] 31–33 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20–7.24 (m, 1 H), 7.78–7.86 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 128.0, 134.7, 135.1, 138.1.

1-Methyl-1*H*-indole-2-sulfonyl Azide (5e)

Pale yellow oil; yield: 30%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.99 (s, 3 H), 7.21–7.30 (m, 1 H), 7.40–7.54 (m, 3 H), 7.76 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.3, 110.5, 112.2, 121.7, 123.2, 124.5, 126.9, 130.8, 139.7.

HRMS: *m*/*z* [M]$^+$ calcd for $C_9H_8N_4O_2S$: 236.0362; found: 236.0357.

2-Furansulfonyl Azide (5f)

Pale yellow oil; yield: 68%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.62–6.64 (m, 1 H), 7.26–7.28 (m, 1 H), 7.70 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 111.9, 119.4, 146.3, 148.2.

HRMS: *m*/*z* [M]$^+$ calcd for $C_4H_3N_3O_3S$: 172.9895; found: 172.9887.

2-Pyridinesulfonyl Azide (5g)[23]

Pale yellow oil; yield: 90%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.70 (m, 1 H), 8.00–8.04 (m, 2 H), 8.80 (d, *J* = 4.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 122.0, 128.3, 138.5, 150.6, 156.9.

1-Methyl-1*H*-imidazole-2-sulfonyl Azide (5h)

Colorless solid; yield: 45%; mp 39–41 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.97 (s, 3 H), 7.12 (s, 1 H), 7.23 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.4, 126.5, 129.9, 140.7.

HRMS: *m/z* [M + H]$^+$ calcd for $C_4H_6N_5O_2S$: 188.0237; found: 188.0238.

2-Benzofuransulfonyl Azide (5i)
Pale yellow solid; yield: 23%; mp 58–60 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (td, *J* = 7.0, 1.0 Hz, 1 H), 7.55–7.68 (m, 3 H), 7.76 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 112.7, 115.1, 123.5, 124.9, 125.2, 129.2, 147.8, 156.2.

Anal. Calcd for $C_8H_5N_3O_3S$: C, 43.05; H, 2.26; N, 18.83. Found: C, 43.45; H, 2.05; N, 18.47.

3-Pyridinesulfonyl Azide (5j)[24]
Pale yellow oil; yield: 45%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (dd, *J* = 8.1, 4.9 Hz, 1 H), 8.24–8.27 (m, 1 H), 8.95–8.97 (dd, *J* = 4.8, 1.1 Hz, 1 H), 9.20 (d, *J* = 2.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 124.1, 135.0, 135.3, 148.0, 155.1.

5-Ethyl-2-furansulfonyl Azide (5k)
Pale yellow oil; yield: 40%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.6 Hz, 3 H), 2.74–2.80 (q, *J* = 7.6 Hz, 2 H), 6.24 (d, *J* = 3.6 Hz, 1 H), 7.19 (d, *J* = 3.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.4, 21.7, 106.9, 120.9, 143.9, 165.1.

HRMS: *m/z* [M + H]$^+$ calcd for $C_6H_8N_3O_3S$: 202.0281; found: 202.0307.

2-Thiazolesulfonyl Azide (5l)
Pale yellow oil; yield: 25%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83–7.84 (m, 1 H), 8.11 (d, *J* = 2.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 126.8, 145.3, 162.6.

HRMS: *m/z* [M + H]$^+$ calcd for $C_3H_3N_4O_2S_2$: 190.9692; found: 190.9675.

5-Methyl-2-thiophenesulfonyl Azide (5m)
Pale yellow oil; yield: 30%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.60 (s, 3 H), 6.85–6.90 (m, 1 H), 7.63 (d, *J* = 3.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.8, 126.5, 134.4, 135.3, 151.6.

HRMS: *m/z* [M]$^+$ calcd for $C_5H_5N_3O_2S_2$: 202.9818; found: 202.9822.

5-Methyl-2-furansulfonyl Azide (5n)
Pale yellow oil; yield: 40%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 6.22–6.25 (m, 1 H), 7.18 (d, *J* = 3.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 108.5, 121.1, 143.9, 160.0.

HRMS: *m/z* [M]$^+$ calcd for $C_5H_5N_3O_3S$: 187.0046; found: 187.0054.

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