ORGANIC LETTERS

2008
Vol. 10, No. 16
3385−3388

Efficient Synthesis of Sulfonyl Azides from Sulfonamides

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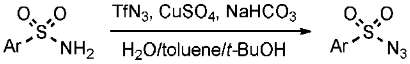
Received May 13, 2008

ABSTRACT



Triflyl azide serves as an efficient diazo transfer reagent in this first direct synthesis of sulfonyl azides from readily available and stable sulfonamides. The process is experimentally simple, mild, and high-yielding. Sulfonyl azides participate in various catalytic transformations providing rapid access to diversely functionalized sulfonamide derivatives in good yields.

Utility of sulfonyl azides in synthesis goes well beyond the commonly used diazo[1] and azide[2] transfer reactions. Their recent applications include a three-component copper(I)-catalyzed coupling with alkynes and amines leading to amidines described by Chang and co-workers,[3] synthesis of *N*-acylsulfonamides via reaction with either thio acids[4] or copper(I) acetylides,[5] and facile preparation of azetidinimines.[6] Unfortunately, the availability of sulfonyl azides has been limited to those accessible from sulfonyl chlorides, which are electrophilic and hydrolytically unstable, and hence have limited functional group compatibility. Sulfonamides, on the other hand, are moisture and air stable, are fairly unreactive toward most functional groups, and are readily available.[7] Therefore, a direct method for the synthesis of sulfonyl azides from sulfonamides would be a welcome addition to the field.

To accomplish this transformation, we envisioned that a sufficiently reactive diazo transfer reagent with a weakly nucleophilic leaving group would favor formation of the azide from the diazo donor reagent and the sulfonamide. Herein, we report a convenient procedure for the direct synthesis of sulfonyl azides from sulfonamides using trifluoromethanesulfonyl (triflyl) azide.

In our initial studies, we subjected the test substrate **1** to the modified diazo transfer conditions of Ernst and co-workers[8] (see Table 1), which uses a ternary mixture of water, toluene, and methanol, obviating the use of dichloromethane[9] typically employed in other triflyl azide preparations.[10] Although this procedure reliably afforded the desired sulfonyl azide product **2**, we found that seemingly identical experiments exhibited disparate yields (entry 1), which we attributed to the poor solubility of the sulfonamide **1**. Switching from methanol to isopropyl alcohol (entry 2) or *tert*-butyl alcohol (entry 3) at the same volumetric ratio improved the solubility of **1** and resulted in improved batch to batch consistency. A scan of inorganic bases revealed that 4 equiv of either bicarbonate (entries 3 and 4) or carbonate (entries 5 and 6) bases resulted in comparable conversions;

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[1] Bollinger, F. W.; Tuma, L. D. *Synlett* **1996**, 407–413.

[2] Panchaud, P.; Chabaud, L.; Landais, Y.; Ollivier, C.; Renaud, P.; Zigmantas, S. *Chem.−Eur. J.* **2004**, *10*, 3606–3614.

[3] Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 2038–2039.

[4] (a) Barlett, K. N.; Kolakowski, R. V.; Katukojvala, S.; Williams, L. J. *Org. Lett.* **2006**, *8*, 823–826. (b) Merkx, R.; Brouwer, A. J.; Rijkers, D. T. S.; Liskamp, R. M. J. *Org. Lett.* **2005**, *7*, 1125–1128.

[5] (a) Cho, S. H.; Yoo, E. J.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16046–16047. (b) Cassidy, M. P.; Raushel, J.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3154–3157.

[6] Whiting, M.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3157–3161.

[7] Compare 24 569 commericially available benzenesulfonamides versus 1385 commercially available benzenesulfonyl chlorides. *SciFinder*, version 2006, Chemical Abstracts Service: Columbus, OH, 2006. (as of January 8, 2008).

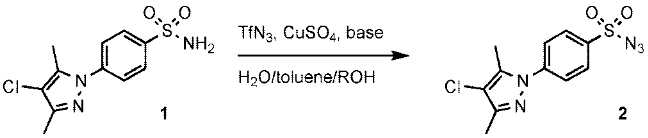
[8] Titz, A.; Radic, Z.; Schwardt, O.; Ernst, B. *Tetrahedron Lett.* **2006**, *47*, 2383–2385.

[9] Use of dichloromethane as a solvent with sodium azide is avoided to prevent inadvertent generation of the highly shock sensitive diazidomethane. See: Peet, N. P.; Weintraub, P. M. *Chem. Eng. News* **1993**, *71*, 4.

[10] (a) Nyffler, P. T.; Liang, C. H.; Koeller, K. M.; Wong, C. H. *J. Am. Chem. Soc.* **2002**, *124*, 10773–10778. (b) Liu, Q.; Tor, Y. *Org. Lett.* **2003**, *5*, 2571–2572.

10.1021/ol8011088 CCC: $40.75

Table 1. Optimization of Reaction Conditions[a]



entry	base	ROH	**1** consumed, %[b]	yield of **2**, %[b]
1	$NaHCO_3$	MeOH	92–97	79–95
2	$NaHCO_3$	*i*-PrOH	92–94	92–93
3	$NaHCO_3$	*t*-BuOH	90–99	85–98
4	$KHCO_3$	*t*-BuOH	98	91
5	Na_2CO_3	*t*-BuOH	>99	95
6	K_2CO_3	*t*-BuOH	>99	92
7	2,6-lutidine	*t*-BuOH	9	ca. 1
8	Et_3N	*t*-BuOH	37	10
9	*i*-Pr_2EtN	*t*-BuOH	79	65
10[c]	$NaHCO_3$	*t*-BuOH	97	97
11[d]	$NaHCO_3$	*t*-BuOH	>99	>99
12[e]	K_2CO_3	*t*-BuOH	>99	>99

[a] 0.1 mmol scale; TfN_3 (ca. 1.0 equiv), $CuSO_4$ (4 mol %), base (4.0 equiv), H_2O/toluene/ROH 1/1.7/6.7. [b] As determined by LC/MS. See Supporting Information for details. [c] Without $CuSO_4$. [d] TfN_3 (ca. 1.5 equiv). [e] Imidazole-1-sulfonyl azide hydrochloride (1.2 equiv).

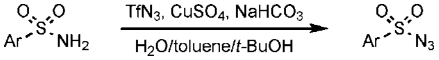
yet, amine bases (entries 7–9) were ineffectual. Although the addition of copper(II) sulfate is not necessary for the reaction to proceed (entry 10), its presence has been demonstrated to mitigate variations in the quality of triflic anhydride, eliminating the need for prior distillation.[11]

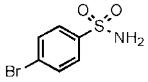
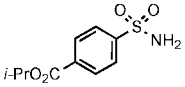
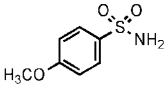
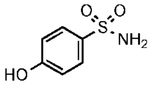
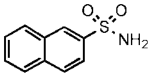
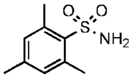
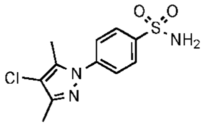
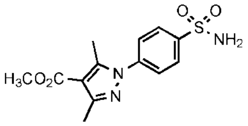
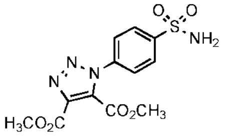
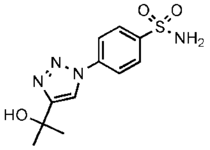
Despite the improvement achieved by altering the solvent, the reaction still did not progress to completion, nor did it produce the azide in consistently high yields across experiments. Consequently, we increased the amount of triflyl azide added (ca. 1.5 equiv, entry 11),[12,13] which resulted in virtually quantitative conversions and consistent performance of the reaction.

Using these modified conditions, complete conversion was typically observed after 15–42 h. If stirring was continued for 72 h, degradation to the corresponding sulfonic acid began to occur.

Although attempts to use tosyl azide, a less reactive diazo transfer reagent, were unsuccessful, imidazole-1-sulfonyl azide,[14] the recently described alternative to triflyl azide, exhibited similarly clean conversions (entry 12), with slight procedural modifications.

Table 2. Aryl Sulfonyl Azides via Diazo Transfer from TfN_3 to Sulfonamides[a]



entry	$ArSO_2NH_2$	time	$ArSO_2N_3$ (yield, %)[b]
1	 **3**	24 h	**4** (74)
2	 **5**	15 h	**6** (94)
3	 **7**	40 h	**8** (86)
4	 **9**	40 h	**10** (89)
5	 **11**	40 h	**12** (86)
6	 **13**	40 h	**14** (90)
7[c]	 **1**	18 h	**2** (93)
8	 **15**	18 h	**16** (75)
9	 **17**	36 h	**18** (92)
10[d]	 **19**	40 h	**20** (53[e])

[a] 1 mmol scale unless otherwise noted; TfN_3 (ca. 1.5 equiv), $NaHCO_3$ (4.0 equiv), $CuSO_4$ (4 mol %), H_2O/toluene/*t*-BuOH 1/1.7/6.7. [b] Isolated yield. [c] 5 mmol scale. [d] 0.5 mmol scale. [e] Starting material (15%) was recovered.

The general procedure[15] has been applied over a range of sulfonamides, and Table 2 illustrates its broad scope. The sulfonyl azide products were typically collected by filtration, after removal of volatiles, or by extraction into ethyl acetate. Both electron-deficient (entries 1 and 2) and electron-rich (entries 3 and 4) sulfonamides were transformed into the corresponding sulfonyl azides in good to excellent yield. The heterocyclic substrates (entries 7–10) are particularly interesting: their complexity would make syntheses of the

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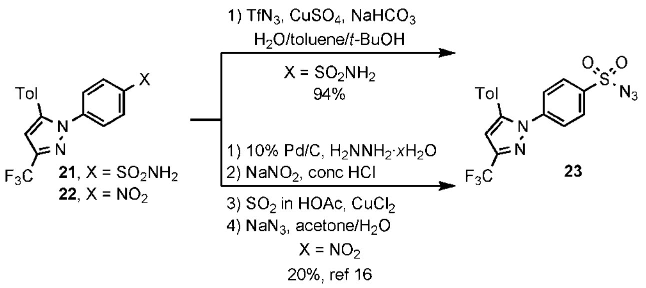
(11) Alper, P. B.; Hung, S. C.; Wong, C. H. *Tetrahedron Lett.* **1996**, *37*, 6029–6032.

(12) To a vigorously stirred ice-cold mixture of NaN_3 (1.30 g, 20.0 mmol), water (5 mL), and toluene (3.3 mL) in a septum-fitted nitrogen flushed scintillation vial, Tf_2O (2.52 mL, 15.0 mmol) was added dropwise. After stirring behind a blast shield for 2 h at 0 °C, the reaction was quenched with saturated aq $NaHCO_3$, and the organic layer was removed. The aqueous layer was extracted with toluene (2 × 3.3 mL). The combined organic extracts were used immediately. A conservative estimate of 50% yield was used for subsequent experiments. See ref 11.

(13) CAUTION: These modifications increase the possibility of excess TfN_3 remaining at the end of the reaction. Before removing the volatiles during the workup, xylenes are placed in the collection trap of the rotary evaporator to prevent collection of neat TfN_3. Before disposal of the solvent in an appropriate fashion, copper powder is added to the xylenes to expedite the degradation of TfN_3.

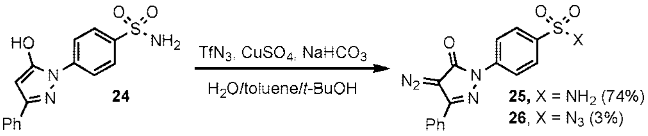
(14) Goddard-Borger, E. D.; Stick, R. V. *Org. Lett.* **2007**, *9*, 3797–3800.

Scheme 1. Elaboration of Celecoxib[a]

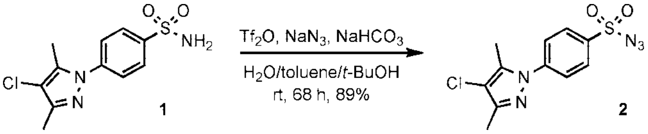


[a] Tol = tolyl.

Scheme 2. C-Nucleophile Preference



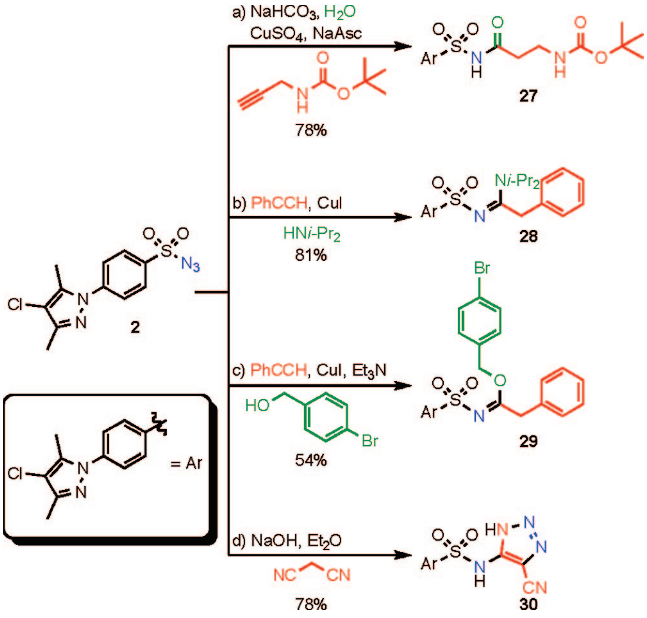
Scheme 3. One-Pot Synthesis of Sulfonyl Azides



corresponding sulfonyl chlorides challenging. This is readily apparent when one compares two syntheses of the sulfonyl azide **23**, as shown in Scheme 1. Whereas the previous preparation of this azide involved a four-step sequence starting from the nitrobenzene derivative **22**[16] in 20% overall yield, the improved procedure makes **23** available in a single step from celecoxib (**21**, Celebrex), which is itself formed from the fusion of 4,4,4-trifluoro-1-*p*-tolylbutane-1,3-dione and 4-hydrazinylbenzenesulfonamide.[17]

As expected, sulfonamides containing carbon nucleophiles, such as **24**, preferentially undergo diazo transfer at the more nucleophilic enol α-carbon, leading to **25** (Scheme 2). Although none of the desired sulfonyl azide was detected, a trace amount of the doubly reacted material **26** was isolated.

Scheme 4. Further Transformations of Sulfonyl Azide **2**[a]



[a] (a) **2** (1.0 equiv), *tert*-butyl prop-2-ynylcarbamate (1.0 equiv), NaHCO$_3$ (1.0 equiv), CuSO$_4$ (0.10 equiv), sodium ascorbate (0.20 equiv), 2:1 *t*-BuOH/H$_2$O; (b) **2** (1.2 equiv), phenylacetylene (1.0 equiv), diisopropylamine (1.2 equiv), CuI (0.10 equiv), THF; (c) **2** (1.2 equiv), phenylacetylene (1.0 equiv), (4-bromophenyl)methanol (1.2 equiv), CuI (0.10 equiv), triethylamine (1.2 equiv), CHCl$_3$; (d) **2** (1.0 equiv), malononitrile (1.0 equiv), NaOH (2.0 equiv), Et$_2$O. NaAsc = sodium ascorbate.

Although the general procedure is more amenable to the synthesis of libraries of sulfonyl azides, a one-pot synthesis whereby a sulfonamide is added directly to the crude reaction mixture of triflic anhydride and sodium azide can be employed (Scheme 3).[18] Omitting CuSO$_4$,[19] triflyl azide was synthesized in situ from Tf$_2$O and NaN$_3$. In this example, the conversion of sulfonamide **1** to sulfonyl azide **2** required 68 h instead of 18 h to reach completion.

Similarly to other sulfonyl azides, **2** undergoes a variety of additional transformations, some of which are shown in Scheme 4. Illustrating the three-component *N*-acylsulfonamide reaction,[5] sulfonyl azide **2** was fused with *tert*-butyl prop-2-ynylcarbamate in an aqueous solvent to form *N*-acylsulfonamide **27**.

Analogously, **2** was reacted with in situ generated copper(I) phenylacetylide and diisopropylamine or (4-bromophe-

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(15) To a mixture of sulfonamide **1** (1.43 g, 5.00 mmol), NaHCO$_3$ (1.68. g), water (6 mL), and 1 M aq CuSO$_4$ (0.20 mL) in a 25 mL Erlenmeyer flask was added a solution of freshly prepared TfN$_3$ (10 mL, 0.75 M in toluene, 7.5 mmol), followed by 40 mL of *t*-BuOH. The flask was loosely capped, and the solution was stirred vigorously behind a blast shield for 18 h at room temperature. The reaction mixture was transferred to a larger round-bottom flask, rinsing with water and toluene. With xylenes in the collection flask, the volatiles were removed by a rotary evaporator, causing precipitation. Filtration afforded **2** as a yellow powder (1.45 g, 93% yield): mp 78.5−79.5 °C, $R_f = 0.46$ (silica gel, hexanes:EtOAc 8:2); $\nu_{\max}$(KBr disc)/cm^{-1} 2138 (N$_3$), 1589, 1503, 1362 (SO$_2$), 1185, 1161 (SO$_2$), 1097, 1028; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.15 (d, $J = 9.0$ Hz, 2H) 7.93 (d, $J = 9.0$ Hz, 2H) 2.43 (s, 3H) 2.24 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 146.7, 144.2, 136.6, 135.2, 128.8, 124.0, 110.4, 11.1, 10.9. Anal. calcd for $C_{11}H_{10}ClN_5O_2S$: C, 42.38; H, 3.23; N, 22.46. Found: C, 42.69; H, 3.39; N, 22.23.

(16) (a) Uddin, M. J.; Rao, P. N. P.; Knaus, E. E. *Bioorg. Med. Chem.* **2003**, *11*, 5273–5280. (b) Habeeb, A. G.; Rao, P. N. P.; Knaus, E. E. *J. Med. Chem.* **2001**, *44*, 3039–3042. (c) Meerwein, H.; Dittmar, G.; Gollner, R.; Hafner, K.; Mensch, F.; Steinfort, O. *Chem. Ber.* **1957**, *90*, 841–852.

(17) (a) Jenning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347–1350. (b) Gosselin, F.; O'Shea, P. D.; Webster, R. A.; Reamer, R. A.; Tillyer, R. D.; Grabowski, E. J. J. *Synlett* **2006**, 3267–3270.

(18) The authors would like to thank a reviewer for suggesting the inclusion of this example.

(19) Wear, J. O. *J. Chem. Educ.* **1975**, *52*, A23–A25.

nyl)methanol, forming amidine[3] **28** and imidate[20] **29**, respectively. Additionally, sulfonyl azide **2** was reacted with malononitrile under aqueous alkaline conditions to form a 5-amino-1-arylsulfonyl-1*H*-1,2,3-triazole-4-carbonitrile (not shown), which under the reaction conditions undergoes a Dimroth rearrangement[21] to the corresponding N*H*-triazole **30**.

The method for the synthesis of sulfonyl azides described here is the first direct, mild, and facile route to sulfonyl azides from readily available and stable sulfonamides. It subverts the cross-reactivity inherent in the traditionally used sulfonyl chlorides, which produce hydrochloric and sulfonic acids upon contact with water, thus causing inadvertent formation of toxic and shock-sensitive hydrazoic acid in the subsequent azidation step. Further transformations of sulfonyl azides illustrate their utility for rapid preparation of densely substituted sulfonamide derivatives.

Acknowledgment. The authors thank Prof. K. B. Sharpless (TSRI) for valuable advice and stimulating discussions, Drs. J. C. Tripp and J. E. Hein (TSRI) for a critical reading of the manuscript, and Dr. A. V. Gontcharov (TSRI) for research samples. Financial support from Novartis (JR graduate fellowship) and the Skaggs Institute for Chemical Biology is gratefully acknowledged.

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8011088

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(20) Yoo, E. J.; Bae, I.; Cho, S. H.; Han, H.; Chang, S. *Org. Lett.* **2006**, *8*, 1347–1350.

(21) (a) Mertz, R.; Van Assche, D.; Fleury, J. P.; Regitz, M. *Bull. Soc. Chim. Fr.* **1973**, *12, Pt. 2*, 3442–3446. For reviews, see: (b) Gilchrist, T. L.; Gymer, G. E. *Adv. Heterocycl. Chem.* **1974**, *16*, 33–85. (c) El Ashry, E. S. H.; El Kilany, Y.; Rashed, N.; Assafir, H. *Adv. Heterocycl. Chem.* **1999**, *75*, 79–167.