ORGANIC LETTERS

1999
Vol. 1, No. 5
783−786

# *tert*-Butylsulfonamide. A New Nitrogen Source for Catalytic Aminohydroxylation and Aziridination of Olefins

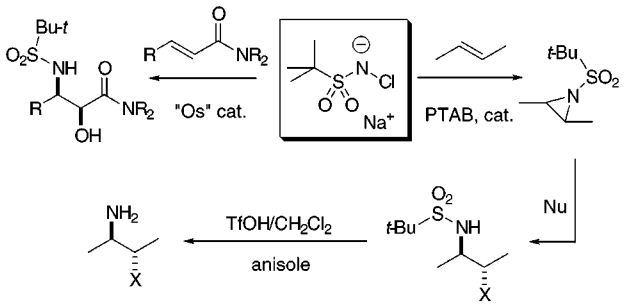
**Alexander V. Gontcharov, Hong Liu, and K. Barry Sharpless***

*Department of Chemistry and the Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037*

*sharples@scripps.edu*

**Received June 23, 1999**

## ABSTRACT




**The *N*-chloramine salt of *tert*-butylsulfonamide has been shown to be an efficient nitrogen source and the terminal oxidant for catalytic aminohydroxylation and aziridination of olefins, resembling closely Chloramine-T by its behavior in these catalytic reactions. The sulfonyl–nitrogen bond in the product or its derivatives is easily cleaved under mild acidic conditions, allowing for facile liberation of the amino group.**

*N*-Chloramine salts of sulfonamides, such as Chloramine-T (TsNClNa) and -M (MsNClNa), have been extensively used as nitrogen sources in both asymmetric and racemic aminohydroxylations, aziridinations, and allylic aminations.[1] However, despite their effectiveness in these reactions, they have a substantial drawback: removal of the alkyl- or arylsulfonyl group from the newly introduced nitrogen substituent requires very harsh conditions.[1b] The *o*-nitrophenylsulfonyl protecting group (Ns), introduced by Fukuyama,[2] is removed under extremely mild conditions and, virtually overnight, became known as the most reliable protecting/activating group for the amines. However, since the nosyl chloramine salts (NsNClNa) have proved less reliable in both catalytic aminohydroxylation and catalytic aziridination processes,[3] we continue to be interested in finding other effective nitrogen sources of the type EWG−N$^-$−X with an easily cleavable EWG−N bond.

Hence, the recent report by Weinreb and co-workers that amines protected with the *tert*-butylsulfonyl group (*t*-Bu$SO_2$ or Bus) can be deprotected under fairly mild acidic conditions[4] led us to try the chloramine salt of *tert*-butylsulfonamide **1** as the nitrogen source in the catalytic processes for aminohydroxylation and aziridination of olefins. The successful outcome is reported here.

**A. Synthesis of *tert*-Butylsulfonamide and Its Chloramine Salt.** The conventional route for synthesis of alkylsulfonamides ($RSO_2NH_2$) concludes with the reaction of

(1) (a) Bruncko, M.; Khuong, T.-A. V.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 454. (b) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451. (c) Rubin, A. E.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2637. (d) Pringle, W.; Sharpless, K. B. *Tetrahedron Lett.* **1999**, in press. (e) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844.

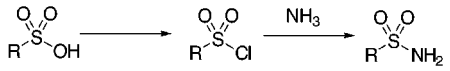
(2) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.

(3) (a) Pringle, W.; Rubin, A. E.; Sharpless, K. B. Unpublished results. (b) However, the nosyl chloramines give excellent results in the stoichiometric selenium-mediated allylic amination (see ref 1a).

(4) Sun, P.; Weinreb, S. M. *J. Org. Chem.* **1997**, *62*, 8604.

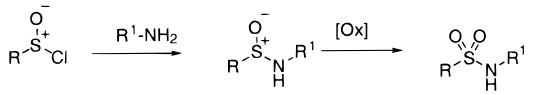
10.1021/ol990761a CCC: $18.00 
**Published on Web 07/30/1999**

ammonia with a sulfonyl chloride, the latter are usually easily prepared from the corresponding sulfonic acids.



This path is efficient for making primary and secondary alkyl sulfonamides as well as aryl and heteroaryl sulfonamides; however, the instability of tertiary alkyl sulfonyl chlorides as well as their principally different mode of reactivity toward nucleophiles[5] render it impractical for most tertiary alkyl sulfonamides. All successful syntheses to date establish the S−N bond in a lower oxidation state sulfur derivative, and *tert*-butylsulfinyl chloride (**2**) has been the intermediate of choice. Sulfinyl chloride **2** is converted to **1** via a straightforward and well-documented two-step sequence: reaction with ammonia yields the relatively stable *tert*-butylsulfinamide **3** which is then oxidized to **1** with a variety of reagents (Scheme 1).

**Scheme 1**

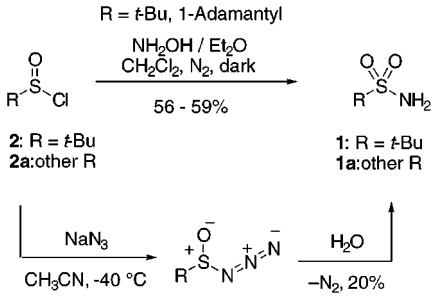


**2**: R = *t*-Bu **3**: R = *t*-Bu, $R^1$ = H **1**: R = *t*-Bu, $R^1$ = H

| Oxidants | Ref. |
|---|---|
| $KMnO_4$ | 6a |
| MCPBA | 4 |
| $RuCl_3/NaIO_4$ | 4 |
| $H_2O_2/LiOH$ | 6b |
| NaOCl/PTC | 6c |

However, there is precedent in the literature that the above sequence can be performed in a single step. Thus Hovius and Engberts[7] found that reaction of **2** with hydroxylamine led directly to sulfonamide **1** (Scheme 2). Unfortunately, the method calls for the use of the free base of hydroxylamine, which is unstable, unsafe, and difficult to handle. Another example, published by Maricich and Hoffman,[8] involved generation of the sulfinyl azide **4a** by reaction of **2a** (R = Ph) with $NaN_3$ at low temperature (Scheme 2). The intermediate **4a** proved explosive when warmed neat; however, its slow decomposition in the presence of water afforded **1a** in 20% yield.

**Scheme 2**



**4a**: R = Ph

We speculated that the latter transformation might become a practical synthetic method if the unstable, and potentially dangerous, sulfinyl azide was not allowed to accumulate in the reaction mixture but was instead converted to the product immediately as formed. Indeed, performance of the reaction in refluxing acetonitrile containing suspended sodium azide and small amounts of water, under dropwise addition of neat sulfinyl chloride **2**, afforded reasonably pure *tert*-butylsulfonamide in 76% yield. The process is highly exothermic, and the addition rate of **2** is adjusted to maintain gentle reflux of the acetonitrile.[9]

The intermediate *tert*-butylsulfinyl chloride was prepared from commercially available bis-*tert*-butyl disulfide in two steps as shown in Scheme 3.[10] The whole reaction sequence was conveniently carried out on a multigram scale.

(5) Stetter, H.;Krause, M.; Last, W.-D. *Chem. Ber.* **1969**, *102*, 3357.

(6) (a) Oppolzer, W.; Wills, M.; Starkemann, C.; Bernardinelli, G. *Tetrahedron Lett.* **1990**, *31*, 4117. (b) Martinez-Merino, V.; Gil, M. J.; Zabalza, J. M.; Gonzalez, A. *Heterocycles* **1995**, *41*, 2737. (c) King, J. F.; Lam, J. Y. L.; Dave, V. *J. Org. Chem.* **1995**, *60*, 2831.

(7) Hovius, K.; Engberts, B. F. N. *Tettrahedron Lett.* **1972**, 181.

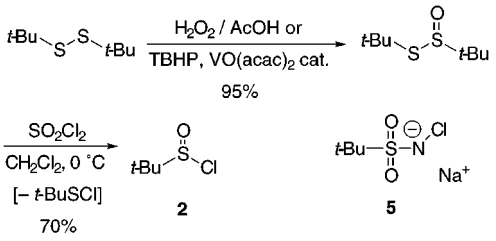
(8) Maricich, T. J.; Hoffman, V. L. *J. Am. Chem. Soc.* **1974**, *96*, 7770.

(9) Sodium azide (16.2 g, 249 mmol) was suspended in 100 mL of acetonitrile and 10 mL of water. The mixture was heated to just below the boiling point of acetonitrile, the source of heat was removed, and *tert*-butylsulfinyl chloride (20 g, 142 mmol) was added slowly to the vigorously stirred mixture. The reaction is highly exothermic, and the addition rate was adjusted to maintain gentle reflux of acetonitrile. After the addition was complete, the reaction mixture was allowed to cool to room temperature. Ethyl acetate (50 mL) and water (40 mL) were added, and the layers were separated. The aqueous layer was extracted once with ethyl acetate, and the combined organic layers were washed with water and dried with $MgSO_4$. After the solvents were evaporated in vacuo, the residue was mixed with 100 mL of ether and the crystals were filtered and washed with ether. The product was recrystallized from acetone to afford 14.5 g (74%) of *tert*-butylsulfonamide as white crystals (mp 161−163 °C, lit.[7] 162−165 °C).

(10) The procedure below is a modification of the synthesis reported in Netscher, T.; Prinzbach, H. *Synthesis* **1987**, 683. (a) A mixture of *tert*-butyl disulfide (89 g, 0.50 mol), vanadyl acetylacetonate (1.33 g, 5.0 mmol), *tert*-butyl hydroperoxide (TBHP, ca. 4.1 M solution in benzene, prepared as described elsewhere,[11] 10 mL), and benzene (250 mL) were stirred for 10 min at 50 °C on a water bath. Then the remainder of the TBHP solution (146 mL, 0.60 mol total) was added slowly so that the temperature inside the reaction flask did not rise above 80 °C. After the addition was complete, the mixture was stirred at 60 °C for 1 h (completion of the reaction was checked by TLC and/or GC) and then chilled in an ice bath. The excess of TBHP was destroyed by treating the mixture with a saturated aqueous solution of sodium metabisulfite (exothermic reaction!). The organic phase was separated and washed with saturated aqueous sodium bicarbonate and brine and then dried with magnesium sulfate. The crude product was isolated in 95% yield (92 g) by evaporating the solvents in a vacuum. The product thus obtained contained traces of unreacted disulfide as the only impurity, and it was used in the subsequent step without further purification. (b) To a solution of *tert*-butyl *tert*-butanethiosulfinate (124 g, 0.64 mol) in 300 mL of methylene chloride, chilled in ice, was added slowly a solution of sulfuryl chloride (86 g, 0.64 mol) in 50 mL of methylene chloride. The resulting yellow solution was stirred for 1 h allowing it to gradually reach room temperature. At this point NMR analysis revealed no starting material remaining. The solvent and volatile byproducts of the reaction were removed under aspirator vacuum at room temperature (stench!). The product was isolated by fractional distillation of the remaining oil (boiling range 65−69 °C at 24 mmHg). Yield: 67 g (75%) as a pale yellow oil. Occasionally, the distilled *tert*-butylsulfinyl chloride was contaminated with side products (most probably, sulfur chlorides), which gave it a deeper yellow or even orange color. The presence of these impurities did not affect the outcome of the next step (ref 9).

(11) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.

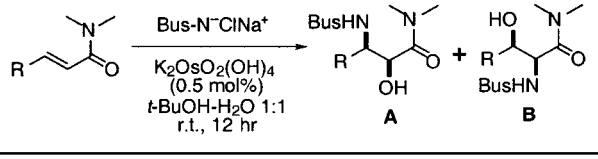
**Scheme 3**

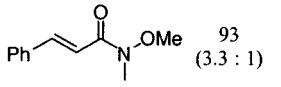
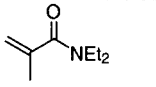
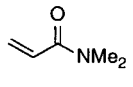
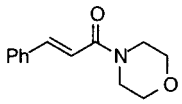
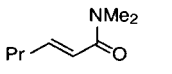
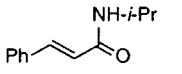
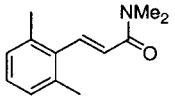
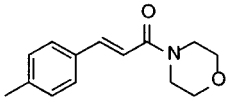
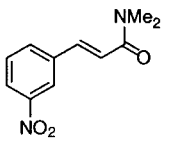
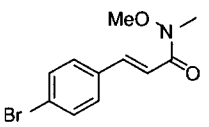



Treatment of **1** with 1 equiv of *tert*-butyl hypochlorite and 1 equiv of sodium hydroxide gave the corresponding chloramine salt **5**[12] which was used as the nitrogen source in all the catalytic oxidative aminations described here.

**B. Aminohydroxylation of α,β-Unsaturated Amides.** Rubin and Sharpless[1c] recently described the very efficient osmium-catalyzed aminohydroxylation of α,β-unsaturated amides with Chloramine-T as the nitrogen source. The turnover rates, chemoselectivities, and yields for this class of substrate proved to be substantially higher than those for any of the other olefin classes already known to undergo aminohydroxylation. In Table 1, we present the results of aminohydroxylation of α,β-unsaturated amides using the new chloramine salt **5** under essentially the same reaction conditions as reported previously using Chloramine-T.[1c,16]

**Table 1.** Aminohydroxylation of α,β-Unsaturated Amides (Reaction Conditions: Olefin, BusNClNa (1.2 equiv), $K_2OsO_2(OH)_4$ (0.5 mol %), *t*-BuOH−$H_2O$ 1:1, rt, 12 h)



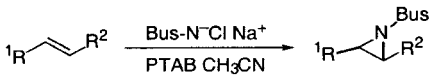

| Starting Alkene | Amino-alcohol yield, % (ratios A : B) | Starting Alkene | Amino-alcohol yield, % (ratios A : B) |
|---|---|---|---|
|  | 93 (3.3 : 1) |  | 90 (A only) |
|  | 84 (A only) |  | 70 (3.1 : 1) |
|  | 91 (2.5 : 1) |  | 71 (2.3 : 1) |
|  | 82 (4.5 : 1) |  | 84 (2.7 : 1) |
|  | 94 (1.5 : 1) |  | 81 (1.8 : 1) |

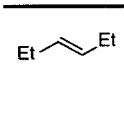
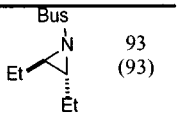
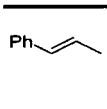
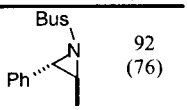
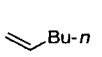
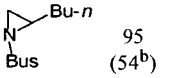
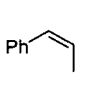
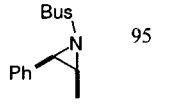
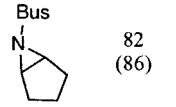
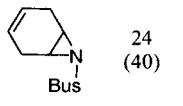
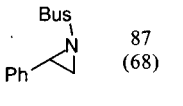
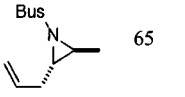
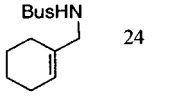
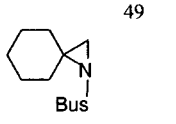
As in the Chloramine-T-based aminohydroxylations, high yields of aminoalcohols resulted and competitive formation of diols was not detected. The regioselectivity of the aminohydroxylation is substrate-dependent but becomes irrelevant if the mixture of these racemic regioisomers is intended for closure to the corresponding aziridine (as described in our previous report,[1c] the isomers A and B converge to give the same racemic aziridine). In the present case, the option for easier liberation of the free amino group should significantly increase the synthetic value of these transformations.

**C. Aziridination of Olefins.** The aziridination of olefins with Chloramine-T-catalyzed by phenyltrimethylammonium tribromide (PTAB)[1e] provides another case where use of Bus-NClNa (**5**) has no deleterious effect on the catalytic process. The aziridinations using **5** (Table 2) were carried out in acetonitrile at room temperature with 10 mol % of PTAB as the catalyst.

As for aminohydroxylation, the results are similar to those obtained in the earlier study with Chloramine-T.[1e] High yields of aziridines are generally observed with simple unfunctionalized olefins. Most often, aziridines are the only reaction

**Table 2.** Aziridination of Alkenes with Bus-NClNa Salt in the Presence of PTAB as a Catalyst (Alkene/Bus-NClNa = 1:1.2 mol, PTAB 10 mol %, MeCN, rt, 10 h)



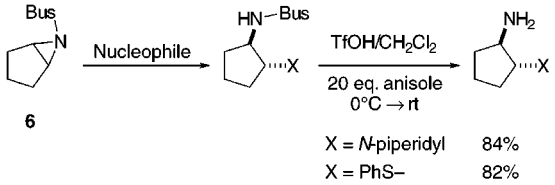

| Alkene | Product | Yield, %[a] | Alkene | Product | Yield, %[a] |
|---|---|---|---|---|---|
|  |  | 93 (93) |  |  | 92 (76) |
|  |  | 95 (54[b]) |  |  | 95 |
|  |  | 82 (86) |  |  | 24 (40) |
|  |  | 87 (68) |  |  | 65 |
|  |  | 24 | | | |
| |  | 49 | | | |

a) Crude isolated yield of the aziridine. Numbers in parentheses indicate the yields observed in aziridination with Chloramine-T (ref. 1e); b) This yield was obtained with 1-dodecene and Chloramine-T.

products, so that product isolation is simple and does not require chromatography. The aziridination is stereospecific: for example, *cis*- and *trans*-$\beta$-methylstyrene give exclusively the *cis*- and *trans*-aziridines, respectively. The exocyclic olefin, methylenecyclohexane, also gave substantial amounts of the rearranged allylic sulfonamide. The low yield of the aziridine from 1,4-cyclohexadiene is likely due to competitive oxidation to the arene, well-precedented in oxidations of this particular diene.

**D. Amine Deprotection.** Two *tert*-butylsulfonamides obtained via a nucleophilic openings of representative aziridine **6** (Scheme 4) were deprotected using the conditions developed by Weinreb.[4] The Bus-protected primary amides gave high yields of the free amines upon treatment with a solution of triflic acid in methylene chloride in the presence of anisole. The product is conveniently separated from the side products by acid−base extractions.

**Scheme 4**




In conclusion, an improved synthesis of *tert*-butyl sulfonamide **1** has been developed and its derived chloramine salt **5** was shown to be an efficient nitrogen source in aminohydroxylation and aziridination of olefins, mirroring closely the behavior of Chloramine-T in these catalytic reactions. As disclosed by Weinreb et al.[4] in the publication that inspired the present study, the *t*-Bu$SO_2$ group is easily cleaved under reasonably mild acidic conditions.

**Acknowledgment.** We thank the National Institute of General Medical Sciences, National Institutes of Health (GM-28384), the National Science Foundation (CHE-9531152), and the W. M. Keck Foundation for financial support and are grateful to A. E. Rubin for helpful discussions.

OL990761A

(12) ***N*-Chloro-*tert*-butylsulfonamide, sodium salt (5)** was prepared according to the procedure analogous to one published previously for $MeSO_2NCl$ Na.[13] *tert*-Butyl hypochlorite[14] (5.54 g, 51.1 mmol) was added slowly to a stirred solution of **1** (7.0 g, 51.1 mmol) in a standardized aqueous solution of sodium hydroxide (0.993 M, 51.1 mmol, 51.5 mL, Aldrich) at room temperature. The resulting mixture was stirred for 1 h and then concentrated to dryness in a vacuum. The solid was triturated with diethyl ether, filtered, and dried in a vacuum oven at 80 °C for 10 h to afford 9.7 g (98%) of the anhydrous **5** as a white powder. Analysis of the product by iodometric titration[15] revealed an available chlorine content of 35.1% (theor. 36.6%).

(13) Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2810.

(14) Mintz, M. J.; Walling, C. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 184.

(15) Titration was performed by following the protocol established for Chloramine T: *Reagent Chemicals: American Chemical Society Specifications*, 8th ed.; American Chemical Society: Washington, DC, 1993; pp 242−244.

(16) All the new compounds were characterized using proton and carbon NMR spectra whose key features closely matched those for the previously reported *N*-tosyl analogues.