Mild Deprotection of Primary *N*-(*p*-Toluenesulfonyl) Amides with SmI_2 Following Trifluoroacetylation

Ziad Moussa, Daniel Romo*

Department of Chemistry, Texas A&M University, P. O. Box 30012, College Station, TX 77842-3012, USA
Fax +1(979)8624880; E-mail: romo@mail.chem.tamu.edu

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Abstract: A mild deprotection method for notoriously difficult to unmask primary *N*-(*p*-toluenesulfonyl) amides was developed during our total synthesis studies toward the marine toxin, gymnodimine. The deprotection occurs at low temperature (–78 °C) under mild conditions by initial activation of the nitrogen with a trifluoroacetyl group, followed by reductive cleavage of the *p*-toluenesulfonyl group with samarium diiodide. The substrate scope and functional group tolerance of this useful N–S cleavage process, which builds on related cleavage processes of other nitrogen–heteroatom bonds, is explored.

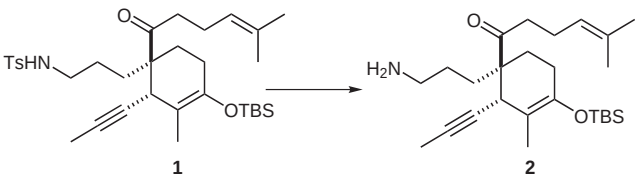
Key words: sulfonamide, samarium diiodide, reductive cleavage, trifluoroacetylation

Arylsulfonyl substituents have found widespread utility in the activation and protection of oxygen and amino groups, respectively.[1] In particular, the *N*-*p*-toluenesulfonyl (tosyl, Ts) group has served as a highly effective protecting group for nitrogen because it is readily introduced and significantly lowers the basicity of nitrogen. In addition, the resulting sulfonamides are generally crystalline, strong chromophores, stable to a variety of reaction conditions, and more resistant to nucleophilic attack than carbamates. However, the tosyl group ranks amongst the most stable of the amino protecting groups, thus requiring harsh conditions for subsequent reductive cleavage. Several early deprotection protocols for the tosyl group involved the use of rather harsh conditions.[2–7] These drastic conditions present functional group incompatiblity and limit the utility of the tosyl group and related protecting groups. The need for milder and neutral reaction conditions prompted recent interest in the development of alternative desulfonylation methods which have included reagents such as refluxing SmI_2 in THF–DMPU,[8] Bu_3SnH–AIBN,[9] magnesium in methanol under ultrasonication conditions[10] and electrolysis (Scheme 1).[11] Important recent developments in this area also include more labile arylsulfonyl protecting groups[12] including the now widely employed *o*- and *p*-nitrosulfonyl (nosyl) group pioneered by the Fukuyama group, which has found widespread use.[13]

Recently, in our efforts toward the total synthesis of gymnodimine, we were faced with the deprotection of a primary sulfonamide **1** to regenerate the amine **2** (Scheme 2).[14]

Scheme 1 Previous methods employed for deprotection of the primary *N*-tosyl group. *Reagents and Conditions*: Na–naphthalenide; HBr–phenol; Na–Hg, Na_2HPO_4; Na–NH_3; SmI_2–HMPA or DMPU; Bu_3SnH–AIBN; Mg–MeOH–sonication; electrolysis

The *N*-tosyl moiety was critical for achieving successful nucleophilic ring opening of this hindered lactam and it also provided the functional group compatibility required for our endgame toward the natural product. Unfortunately, despite numerous methods available for the cleavage of the tosyl group, these proved ineffective, returning either starting material or complex mixtures of products due to functional group incompatibility. While secondary (N,N-disubstituted) sulfonamides may undergo facile cleavage in many cases, the analogous primary (N-monosubstituted) sulfonamides are notoriously difficult to unmask. Thus, we became interested in developing a mild method for removal of the tosyl group from primary sulfonamides.



Scheme 2 Required *N*-tosyl deprotection in a model sulfonamide **1**

The application of samarium diiodide (SmI_2) as a one-electron-transfer reagent has been extensively studied and its functional group compatibility has been well documented.[15] While the SmI_2–DMPU system was previously reported by Vedejs to cleave arenesulfonamides, it was limited to only a few substrates and worked best with the *N*-(phenylsulfonyl) group and N,N-disubstituted sulfonamides.[8] Building on this work, Parsons recently reported the desulfonylation of N-sulfonyl amides without an additive using samarium diiodide.[16] This latter procedure required isolation of the sulfonamides, the use of the rather robust benzoyl group as an activating group, and the requirement of warming to room temperature to achieve desulfonylation. Prior to Parsons's work, Keck and subsequently Marco–Contelles reported an efficient process for the reductive cleavage of N–O bonds of acylated hydroxylamines and hydroxamic acid derivatives using SmI_2.[17]

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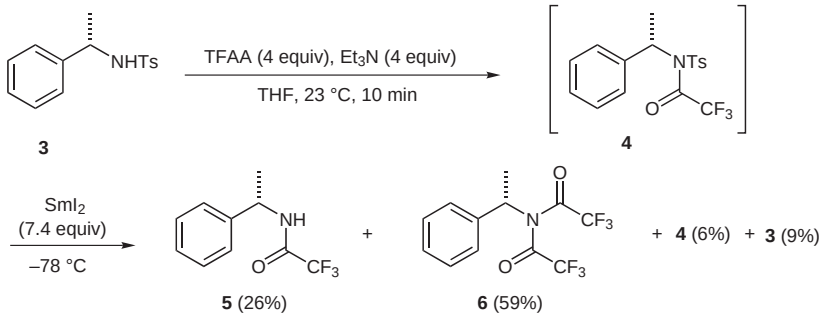
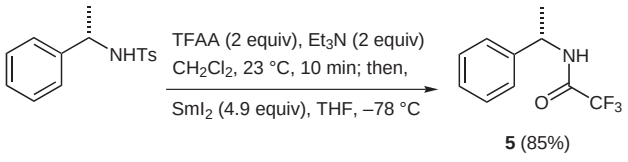


Scheme 3 One-pot reductive cleavage of a sulfonamide

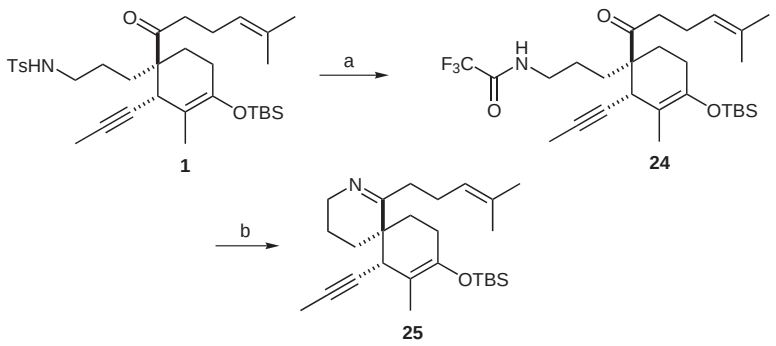
The acyl function was originally utilized to obviate isolation difficulties associated with low molecular weight primary amines and their inherently polar nature.[17a] However, recent studies have suggested that the acyl substitutent allows for reductive cleavage at lower temperatures and leads to greatly improved yields.[17b] Furthermore, a related, mild N–O cleavage with SmI_2 was employed by us in our pateamine A synthesis.[18] Based on these precedents and in conjunction with our studies toward gymnodimine,[14] we proceeded to investigate the cleavage of N–S bonds of acylated N-monosubstituted sulfonamides with SmI_2. The trifluroacetyl group was of particular interest and represented an attractive activating group due to its ease of installation, expected activation leading to low temperature N–S bond cleavage,and mild removal (e.g. NH_3–MeOH). The use of the trifluoroacetyl group contrasts to related methods employing a *tert*-butoxycarbonyl (Boc) activating group which require room temperature cleavage with Mg and sonication which could be useful if a protecting group switch is required and the Boc group is to be carried through additional steps.[10] We now report the development of a mild and convenient method for the deprotection of N-monosubstituted aryl- and alkylsulfonamidesinvolving initial N-acylation/activation with trifluoroacetic anhydride (TFAA) followed by direct reductive cleavage with SmI_2 at –78 °C.[19]

We were initially interested in developing a one-pot procedure involving in situ acylation of N-monosubstituted sulfonamides with TFAA, followed by treatment with SmI_2. (*S*)-*N*-(1-Phenylethyl) toluenesulfonamide (**3**) was employed as a model substrate since it is readily prepared and presents a more sterically encumbered α-substituted amine. Employing tetrahydrofuran as solvent for both operations, we screened several bases (NaH, DBN, DBU, 2-*tert*-butyl-1,1,3,3-tetramethylguanidine and Et_3N) and determined that efficient acylation of amine **3** required the use of four equivalents of both triethylamine and TFAA (Scheme 3). The extent of conversion to amide **4** was readily monitored by aliquot NMR and complete acylation was observed within ten minutes as indicated by the complete disappearance of the N–H proton and other diagnostic signals of amine **3** and the appearance of new signals that had the characteristic downfield shift expected upon N-acylation (δ = 0.80–1.04 ppm). For example, the chemical shift of the methine proton of amide **4** (q, δ = 5.52 ppm, *J* = 7.0 Hz) exhibited a Δδ of 1.0 relative to sulfonamide **3** (app. quintet, δ = 4.48 ppm, *J* = 7.0 Hz).

Surprisingly, when the *N*-trifluoroacetylsulfonamide intermediate **4** was treated with excess SmI_2 (7.4 equiv) at –78 °C and the crude mixture was analyzed by ^1H NMR, only ca. 26% of the desired trifluoroacetamide **5** was present relative to other products (Scheme 3). The major component of the reaction mixture was the bistrifluoroacetamide derivative **6** (59%) presumably resulting from subsequent trifluoroacetylation following reductive cleavage.[20] In addition, unreacted *N*-trifluoroacetylsulfonamide **4** and sulfonamide **3** comprised 6% and 9% of the mixture, respectively. Clearly, the presence of excess amounts of TFAA and triethylamine is not desirable. Thus, in order to suppress the subsequent acylation of the product we initially attempted to isolate and purify (SiO_2) the intermediate *N*-trifluoracetylsulfonamide prior to treatment with SmI_2 and remove excess reagents by chromatography. Unfortunately, the acetylated intermediates generally proved very labile undergoing cleavage of the trifluoroacetamide group during workup and purification. After extensive investigation of solvents and bases, we found that a significant reduction in the amount of reagents required for complete acetylation could be achieved with dichloromethane as solvent. In this case, two equivalents of TFAA and triethylamine resulted in complete trifluoroacetylation at 23 °C within ten minutes. Since dichloromethane is not an ideal solvent for SmI_2 reactions and unreacted TFAA remains, excess TFAA (bp 39–40 °C) and triethylamine (bp 88 °C) were removed by concentration in vacuo followed by addition of tetrahydrofuran. Under these conditions, the desired trifluoroacetamide **5** was isolated in 85% yield (99%, based on recovered sulfonamide **3**), following treatment of the intermediate *N*-trifluoroacetylsulfonamide with 4.9 equivalents of SmI_2 (Scheme 4). The spectral and physical data



Scheme 4 Optimized conditions for reductive cleavage of a sulfonamide



Scheme 5 *Reagents and conditions*: (a) $(CF_3CO)_2O$, Et_3N, THF, then SmI_2, 63%; (b) $NH_3 \cdot H_2O$, MeOH, 80 ºC, 89%.

for amide **5** were in accord with spectral and physical data reported in the literature.[21]

In order to investigate the scope and limitations of this procedure, we examined the trifluoroacetylation and reductive cleavage of several primary *N*-tosyl sulfonamides (Table 1).[22] The aryl- and alkylsulfonamides used as starting material in this work were prepared from commercial primary amines by standard conditions.[23] With the exception of substrate **8** (entry 3), all the sulfonamides shown in Table 1 underwent clean and complete trifluoroacetylation according to the established conditions.[24] Subsequent treatment with SmI_2 at –78 °C typically afforded good to excellent yields of the desired trifluoroacetamides, (60–95%).[22] As can be seen in Table 1, the deprotection method was useful for a variety of substrates and compatible with a wide range of functional groups including carbamates, bromides, acetals, nitriles, ketones, lactones, and lactams. Detosylation of the relatively hindered α-substituted sulfonamide **3** (entry 1) and *N*-Boc-piperidine sulfonamide **7** (entry 2) produced the corresponding acetamides in high yields without cleavage of the carbamate group in the latter case. When the reaction of the bromosulfonamide **8** (entry 3) was conducted at 23 °C, the isolated yield was low (24%), presumably due to reduction of the primary bromide. However at –78 °C, the reduction was highly chemoselective providing acetamide **17** in excellent yield (88%).[25] Similarly, *N*-piperonyl-*p*-toluenesulfonamide **9** and its cyanobenzyl derivative **10** underwent smooth cleavage (entries 4 and 5). We also examined the detosylation of arylsulfonamides **14** and **15** (entries 9 and 10) and these deprotections proceeded readily, albeit in lower yields with respect to alkylsulfonamides. In the former case, the low yield (71%) was due to incomplete detosylation and recovery of sulfonamide **14** (yield of acetamide **23** was 77% based on recovered sulfonamide **14**).

Finally, we previously demonstrated the applicability of this approach to the gymnodimine intermediate, sulfonamide **1**, possessing a labile silyl enol ether. Importantly, we were able to perform a one-pot activation–deprotection without the need of removing excess reagents and switching solvents (Scheme 5).[14] This demonstrates the utility of this approach and the feasibility of performing detosylation in a single operation. The resulting acetamide **24** was converted in one step into the desired cyclic imine under basic conditions.

In summary, we have developed an improved and more general method for deprotection of primary *N*-toluenesulfonamides at low temperature building on previous related reductions of N–S and N–O bonds. This one-pot method should find utility in synthesis due to the mild reaction conditions employed, excellent chemoselectivity, and high yields obtained with a variety of alkyl and aryl *N*-sulfonamides. In addition, this deprotection protocol should prove successful with other types of sulfonamides. Finally, unmasking of the trifluoroacetamides to the corresponding aliphatic and aromatic amines is facile and readily accomplished using several published methods thus providing access to the parent amines.[26]

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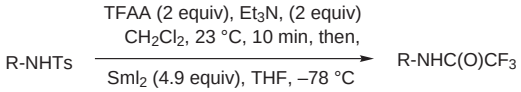
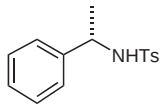
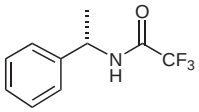
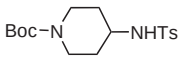
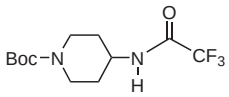
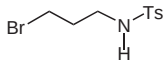
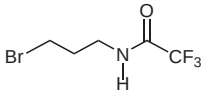
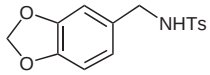
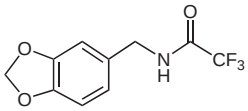
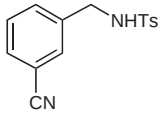
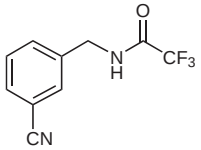
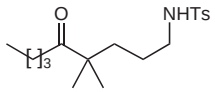
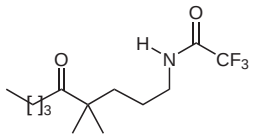
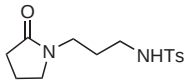
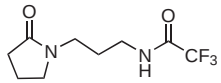
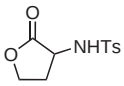
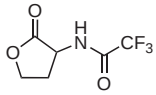
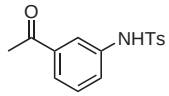
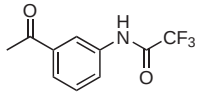
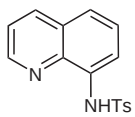
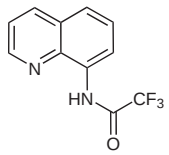
Table 1 Deprotection of Primary Sulfonamides via Trifluoroacetylation and Reductive Cleavage with SmI_2



Entry	Substrate	Product	Yield (%)
1	 **3**	 **5**	85
2	 **7**	 **16**	95
3[a]	 **8**	 **17**	88
4	 **9**	 **18**	84
5	 **10**	 **19**	85
6	 **11**	 **20**	82
7	 **12**	 **21**	95
8	 **13**	 **22**	77
9	 **14**	 **23**	71
10	 **15**	 **24**	60

[a] In this case, Et_3N (3 equiv) and TFAA (3 equiv) were used.

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(19) SmI_2 was prepared according to the published procedure, see: Imamoto, T.; Ono, M. *Chem. Lett.* **1987**, 501.
(20) We were unable to isolate a clean sample of bistrifluoroacetamide **6** as it underwent partial deacetylation to acetamide **5** during chromatography.
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(22) The following compounds are known and spectroscopic data have been previously reported in the literature: (a) Sulfonamide **3**: Soeta, T.; Nagai, K.; Fujihara, H.; Kuriyama, M.; Tomioka, K. *J. Org. Chem.* **2003**, *68*, 9723. (b) Sulfonamide **8**: Di Martino, A.; Galli, C.; Gargano, P.; Mandolini, L. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1345. (c) Sulfonamide **9**: Moon, B.; Han, S.; Yoon, Y.; Kwon, H. *Org. Lett.* **2005**, *7*, 1031. (d) Sulfonamide **10**: Bookser, B. C.; Bruice, T. C. *J. Am. Chem. Soc.* **1991**, *113*, 4208. (e) Acetamide **16**: Mach, R. H.; Luedtke, R. R.; Unsworth, C. D.; Boundy, V. A.; Nowak, P. A.; Scripko, J. G.; Elder, T.; Jackson, J. R.; Hoffman, P. L.; Evora, P. H.; Rao, A. V.; Molinoff, P. B.; Childers, S. R.; Ehrenkaufer, R. L. *J. Med. Chem.* **1993**, *36*, 3707. (f) Acetamide **17**: Strømgaard, K.; Brierley, M. J.; Andersen, K.; Sløek, F. A.; Mellor, I. R.; Usherwood, P. N. R.; Krogsgaard-Larsen, P.; Jaroszewski, J. W. *J. Med. Chem.* **1999**, *42*, 5224. (g) Acetamide **18**: Keck, G. E.; Wager, T. T.; McHardy, S. F. *Tetrahedron* **1999**, *55*, 11755. (h) Acetamide **24**: Vangapandu, S.; Jain, M.; Jain, R.; Kaur, S.; Singh, P. P. *Bioorg. Med. Chem.* **2004**, *12*, 2501. (i) **General Procedure for the Reductive Cleavage of the Tosyl Group of Monosubstituted *N*-(*p*-Toluenesulfonyl) Amides as Described for Preparation of Amide 5**: To a stirred solution of sulfonamide **3** (55.1 mg, 0.20 mmol) and Et_3N (60 μL, 0.40 mmol) in CH_2Cl_2 (3.0 mL) was added TFAA (57 μL, 0.40 mmol) dropwise via syringe. After aliquot NMR analysis indicated complete reaction (ca. 10 min), the solvent was concentrated in vacuo and the residue was diluted with THF (1.0 mL), cooled to –78 °C and subsequently treated dropwise with SmI_2[19] in THF (10.0 mL, 0.098 M, 0.98 mmol). The resulting mixture was stirred for 30 min and then quenched by filtering through a compressed pad of silica gel. The filter pad was washed with EtOAc and the solvent was removed in vacuo. The residue was chromatographed (elution with 10% EtOAc–hexanes) to afford acetamide **5** (37 mg, 85%) as a white solid, followed by the starting material **3** (7.5 mg). The spectral data for the isolated material was in accord with published spectral data.[21]
(23) Et_3N was not suitable for the tosylation of 3′-aminoacetophenone (Table 1, sulfonamide **14**) as it resulted in an inseparable mixture of **14** and its bistosylated derivative. However, employing pyridine as a base led to exclusive monotosylation.
(24) Substrate **8** (Table 1, entry 3) required TFAA (3 equiv) and Et_3N for complete acetylation.
(25) Reductive cleavage of the tosyl group at 23 °C led to significantly reduced yields of trifluoroacetamide.
(26) (a) Weygand, F.; Swodenk, W. *Chem. Ber.* **1957**, *90*, 693. (b) Newman, H. *J. Org. Chem.* **1965**, *30*, 1287. (c) Quick, J.; Weygand, F.; Frauendorfer, E. *Chem. Ber.* **1970**, *103*, 2437. (d) Barrett, A. G. M.; Lana, J. C. A. *J. Chem. Soc., Chem. Commun.* **1978**, 471. (e) Meltz, C. *J. Org. Chem.* **1979**, *44*, 573. (f) Eckstein, F. *J. Org. Chem.* **1979**, *44*, 2049. (g) Pyne, S. G. *Tetrahedron Lett.* **1987**, *28*, 4737. (h) Bergeron, R. J.; McManis, J. J. *J. Org. Chem.* **1988**, *53*, 3108. (i) King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1994**, *116*, 562. (j) Imazawa, M.; Albanese, D.; Corcella, D.; Landini, A.; Maia, A.; Penso, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 247. (k) Kudzin, Z. H.; Lyzwa, P.; Luczak, J.; Andrijewski, G. *Synthesis* **1997**, 44.