ORGANIC LETTERS

2009
Vol. 11, No. 3
503−506

Instantaneous Deprotection of Tosylamides and Esters with SmI_2/Amine/Water

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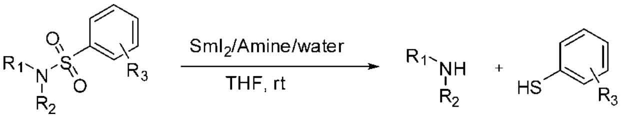
Received September 26, 2008

ABSTRACT



SmI_2/amine/water mediates instantaneous cleavage of tosyl amides and tosyl esters. Highly hindered, sensitive and functionalized substrates were successfully deprotected in near quantitative yield.

Protection and subsequent deprotection of amines and alcohols is a routine procedure employed in almost any multistep synthesis and one of the most versatile protecting groups for amines and alcohols are based on sulfonamide/ester formation (-Ts). The sulfone amides and sulfone esters display desirable properties such as stability under a range of reaction conditions and ease of purification. However, the robustness, especially for the tosyl amides derived from alkylamines, can be a major disadvantage since it can be notoriously difficult to efficiently deprotect the amines. The traditional deprotection protocols involve the use of lithium or sodium as one-electron donors in combination with various electron carriers. There are also several known methods that are based on acid hydrolysis of the ester or amide bond with strong acids like HBr or $HClO_4$. However, both methods of deprotection suffer from the harsh reaction conditions which likely affects other sensitive functional groups present in the protected compound.[1]

Hence, there has been much interest in the development of alternative methods where milder and possibly more selective reagents are employed. Among those methods reported to mediate tosyl cleavage are: electrolysis,[2] Ni(0)acac/iPrMgCl,[3] Bu_3SnH/AIBN,[4] Mischmetal/$TiCl_4$,[5] Mg/MeOH,[6] Mg/Me_3CoLi,[7] and Na/K metal on silica.[8] Deprotection of tosyl amides employing SmI_2/HMPA or SmI_2/DMPU in refluxing THF have also been reported,[9] and there are examples of deprotections of N-acyl N-tosyl amides using SmI_2 or SmI_2 in combination with aliphatic alcohols.[10] Thus, the primary literature contains a large number of methods indicating the importance of facile deprotection protocols.

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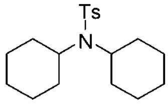
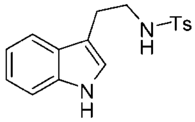
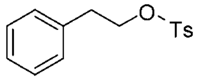
10.1021/ol802243d CCC: $40.75

Even so, many of these methods are nongeneral, are irreproducible, or require special equipment.

Recently we have found that the combination of the mild reducing agent SmI_2, an aliphatic amine (typically pyrrolidine, triethylamine or isopropyl amine) and water is a very powerful reductant that shares properties with the Birch reagent and might therefore serve as an alternative for deprotection of the tosyl group.[11] Herein we wish to communicate our findings that a mixture of SmI_2/amine and water in THF instantaneously deprotects aryl sulfonate esters and amides in unprecedented high yields.

At first we optimized the reaction conditions for the $SmI_2/R_3N/H_2O$ mediated cleavage of the tosyl group from simple amines and alcohols. For this we studied two tosylated amines and a tosylated alcohol, which upon deprotection give fairly nonvolatile compounds, with a minimum risk of mechanical loss during work up (Table 1). Increasing amounts of samarium diiodide, pyrrolidine and water were used in the reaction and the optimum yield in the deprotection was reached with 6 equivalents of SmI_2, 12 equiv of pyrrolidine and 18 equiv of water. In theory, 2 equiv of SmI_2 is needed for breaking the N−S bond, therefore the products of the initial S−N bond cleavage are reduced more rapidly than the tosyl amide itself. Hence the reaction requires a large excess of SmI_2 for completion. In the reaction mixture after complete deprotection of the tosyl amide we observed 4-methylbenzenethiol and the corresponding disulfide.[12]

Table 1. Optimization of the Reaction Conditions[a]

entry	starting material	eq. SmI_2	yield[b]
1		2	62
2		4	90
3		6	96
4		2	29
5		4	67
6		6	95[c]
7		2	31
8		4	64
9		6	95

[a] To a solution of SmI_2 in THF (4 mL, 0.13 M, 0.52 mmol) the tosylester was added followed by water (3 equiv relative SmI_2) and pyrrolidine (2 equiv relative SmI_2). [b] Isolated yields. [c] Experiment performed with 2.6 mmol SmI_2.

The reductive cleavage of the tosyl group occurs instantaneously at room temperature, within seconds the amide or ester is consumed according to GC analysis, and the reaction appears to be quantitative. The reaction does not seem to suffer from steric hindrance (dicyclohexyl amine) and in addition the deprotection works equally well for both primary and secondary tosyl amides (Table 1, entries 1−6). Analogous result was obtained for the tosyl protected alcohol (Table 1, entries 7−9).

We observed no difference in reactivity between aromatic, benzylic or aliphatic amines and found that these model substrates responded equally well to the reagent furnishing the free amines after workup (Table 2, entries 1−3). Although $SmI_2/R_3N/H_2O$ is known to be a powerful reductant that reacts with most functional groups, in practice only carbonyl and related groups (e.g., ketone, aldehyde, nitriles and nitro groups) undergo instantaneous reduction.[11a,b,e,f,h,k] Thus, based on a large difference in kinetics a very high degree of chemoselectivity can still be observed, for example, we know that an alkyl iodide is dehalogenated in the presence of an N-Boc group.[13] Furthermore, an aliphatic nitro group is reduced to the amine in precence of an aromatic chlorine with SmI_2/pyrrolidine/H_2O.[11k]

To test the selectivity toward other functional groups, we prepared a range of tosyl amides containing additional functional groups such as aromatic chlorine, N-Boc, and ketone masked as an ethylene acetal (Table 2, entries 4−6). Pleasingly, deprotection with these functional groups present was successful, and the resulting amines were recovered in close to quantitative yield.

In the course of this work we also examined the cleavage of the N−S bond in N-tosylaziridines as they are considered notoriously difficult to deprotect giving various ring opened byproduct with traditional methods. Vedejs and Lin reported successful cleavage of very sterically hindered tosyl aziridines with SmI_2/DMPU, but with the less hindered N-tosyl-2-phenylaziridine they observed a fast reaction but they could not isolate any of the expected aziridine. Alonso and Andersson have reported that tosyl aziridines undergo a rapid ring opening reaction with the SmI_2/DMPU system, while the use of Mg/MeOH for deprotection gave according to their findings much better results.[9b]

To our delight, we found that both N-tosyl-2-phenylaziridine and N-tosyl-2-benzylaziridine underwent clean and instantaneous deprotection giving nearly quantitative yield of the N−H aziridine using $SmI_2/Et_3N/H_2O$. We also found that the amine used as an additive had a large impact on the outcome of the deprotection of N-tosylaziridines. The use of pyrrolidine and isopropylamine gave no isolated product

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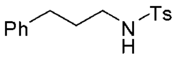
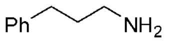
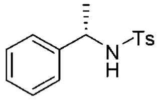
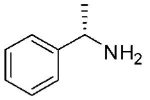
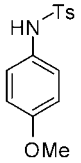
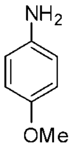
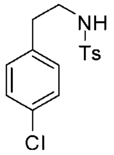
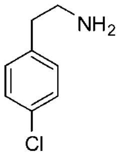
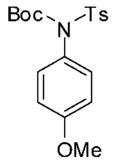
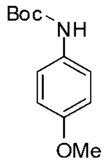
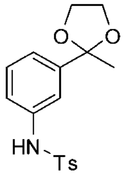
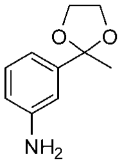
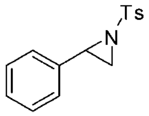
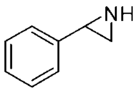
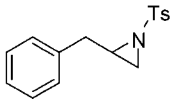
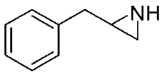
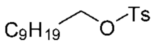
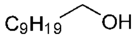
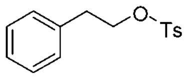
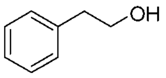
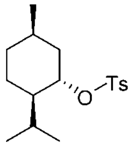
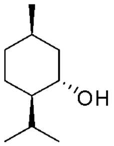
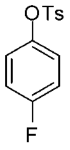
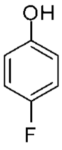
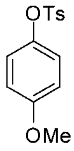
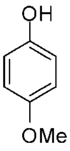
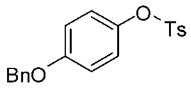
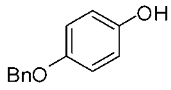
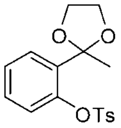
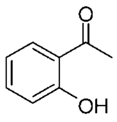
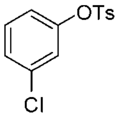
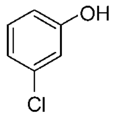
Table 2. SmI_2/Pyrrolidine/Water Mediated Cleavage of Tosyl Amides

entry	starting material	product	yield[a]
1			95
2			98
3			95
4			96
5			94[b, c]
6			95[b]
7			93[d]
8			94[d]

[a] Yield determined with GC/MS analysis comparing to an internal standard. [b] Isolated yield. [c] Performed with 2.6 mmol SmI_2. [d] Triethylamine was used instead of pyrrolidine.

Table 3. SmI_2/Pyrrolidine/Water Mediated Cleavage of Tosyl Esters

entry	starting material	product	yield[a]
1			95
2			95
3			94
4			95
5			95
6			85
7			96
8			93

[a] Yields determined with GC/MS analysis comparing to an internal standard.

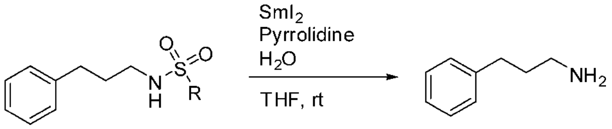
while triethylamine as additive afforded the wanted product in excellent yield (Table 2, entries 7 and 8).

Both tosyl protected alipahtic and aromatic alcohols were efficiently cleaved, leaving the alcohol in excellent yield (Table 3). Electronic properties does not seem to influence the reaction, as there is no difference in yield between the 4-methoxy and 4-fluoro substituted phenyl tosyl esters (Table 3, entries 4−5). This is in contrast to Narender et al. that previously reported that electron-poor aromatics are cleaved with lower effeciency with Mg/MeOH.[6b] Again we prepared a series of protected phenols with slightly more sensitive functionalities (Table 3, entries 6−8) and found that a benzyl ether, an aromatic chlorine and a benzylic ethylene acetal are all compatible with the reaction conditions. Conveniently, the acetal was hydrolyzed during the acidic workup used for the tosyl ester substrates.

To investigate the scope even further for this cleavage reaction, a series of different sulfonate esters and amides were synthesized and we found that the methyl and trifluoromethyl (mesyl- and triflyl- respectively) derivatives gave no detectable product formation (Table 4, entries 1 and 2). The bulkier and more electron-rich sulfone amides (Table 4, entries 3−5) displayed properties similar to -Ts but they were cleaved with slighly lower effeciency. The GC/MS analysis after work up of entries 3−5 in Table 4 revealed that much of the sulfide was desulfurized yielding mesitylene, triisopropylbenzene and anisole in the reaction mixture. This side reaction clearly demands more SmI_2, and therefore, the yield is slightly lower.

The facile cleavage of the aromatic sulfone amides and esters while mesyl amides and mesyl esters are stable to the reagent mixture indicate that the practical reduction potential of $SmI_2/R_3N/H_2O$ is within this regime.[11j] Mechanistically

Table 4. SmI_2/pyrrolidine/water Mediated Cleavage of Alkyl and Aryl Sulfonates



entry	R	yield[a]
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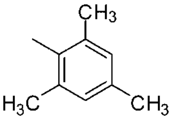
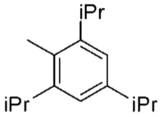
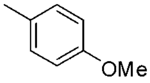
2	CF_3	0
3		95
4		85
5		85

[a] Yield determined with GC/MS comparing to an internal standard.

we propose that one electron is transferred from Sm(II) to the aromatic ring of the sulfone. This may rearrange and accept one more electron leading to fission of the N−S bond (Figure 1). The nonaromatic sulfone amides (i.e., mesylate and triflate) are not capable of this, thus no cleavage reaction is observed.

A new synthetic procedure will never have any impact if it is not practically useful and scalable hence we also demonstrated that this deprotection can be carried out at a larger scale and under standard laboratory conditions. A THF solution of SmI_2 (20 mL, 2.6 mmol, 0.13 M) was freshly prepared from samarium (3.2 mmol) and diiodoethane (2.6 mmol) in a septum capped vial using undried reagents. The vial was loaded with water and the tosyl amide (0.43 mmol) before the amine was added. Immediately after the addition the reaction mixture was subjected to standard workup and the amine was recovered in nearly quantitative yield.

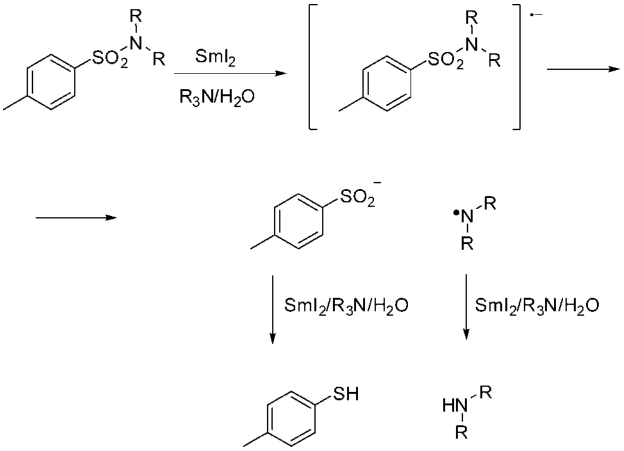


Figure 1. Proposed mechanism for the reductive cleavage of tosyl amides.

To conclude we have developed a highly useful procedure for efficient and very rapid deprotection of tosyl amides and esters to form the corresponding amines and alcohols. The method appears to be general and give consistently high yields with all substrates tested including sterically hindered aliphatic tosyl amides as well as highly sensitive ones like the tosylated aziridines.

Acknowledgment. Financial support from the Swedish Natural Science Council is gratefully acknowledged. Prof. Per-Ola Norrby and Prof. Öjvind Davidsson are acknowledged for valuable comments.

Supporting Information Available: A complete description of experimental details and spectral charateristics of staring materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802243D