Desulfonylation of Amides Using Samarium Iodide

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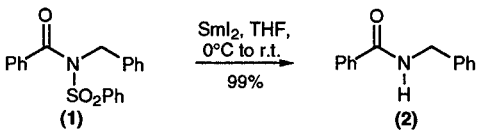
Abstract: The desulfonylation of *N*-sulfonyl amides can be achieved in reasonable to excellent yield by reaction with samarium(II) iodide (SmI_2) in THF at room temperature. Deprotection of acyclic and cyclic amides bearing aryl and alkylsulfonyl groups is possible.

Samarium(II) iodide (SmI_2) is an extremely useful and versatile reagent in synthesis.[1] It acts as an oxophilic one-electron reducing agent (especially in THF and THF-HMPA solution) which is capable of the selective reduction of a variety of functional groups under mild and neutral reaction conditions. This has led to the use of this reagent in deprotection chemistry. Thus, for example, SmI_2 has recently been used to deprotect arene- and pyridine-2-sulfonamides,[2,3] deacylate and dealkyloxycarbonylate protected alcohols and lactams[4] and cleave the N-O bond of free or *N*-acyl *O*-alkylhydroxylamines.[5] In some cases the deprotections require heating and the addition of a cosolvent such as DMPU or a proton source (to increase the reductive potential of SmI_2). We now wish to report the novel application of SmI_2 (without an additive) in the deprotection of *N*-sulfonyl amides, on warming from 0°C to room temperature, to give secondary amides. Previously reported methods for this deprotection can require drastic reaction conditions (*e.g.* HBr or Na/NH_3) which often limit the scope of these procedures.[6,7]

Initial studies centred on the reaction of the *N*-benzenesulfonamide (**1**) (prepared on sulfonylation followed by acylation of benzylamine) using 3 equivalents of SmI_2 in THF[8] at 0°C (see scheme 1).[9] The deprotection was extremely rapid and thin layer chromatographic analysis indicated the consumption of starting material immediately after the addition of the SmI_2. Workup and column chromatography afforded the desired secondary amide (**2**) in an excellent 99% yield.[10] It is of interest to note that there was no evidence for the deoxygenation of the product, *N*-benzylbenzamide (**2**), to dibenzylamine as observed using Sm/SmI_2 in boiling THF.[11]

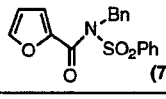
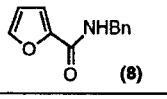
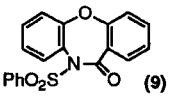
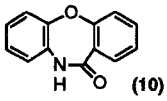
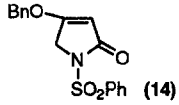
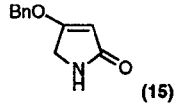
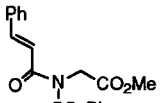
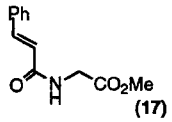
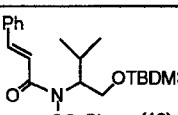
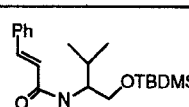


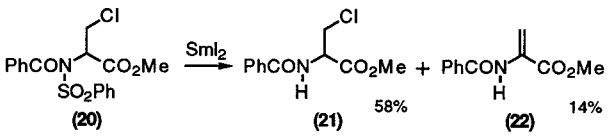
Scheme 1

The generality of this methodology was then investigated as shown in the table. Thus the deprotection of other aromatic and aliphatic sulfonyl groups could be achieved to give amide (**2**) (entries 1 and 2). The N-S bond of the *N*-tosyl derivative (**3**) was cleaved in 87% yield while the methylsulfonamide (**4**) was deprotected in 71% yield. Reaction of the pivaloyl derivative (**5**) was also successful and, although the reaction was slower[12] than those shown earlier, the desired amide (**6**) was isolated in 57% yield (entry 3). The furfuroyl derivative (**7**) and oxazepinone (**9**) (entries 4 and 5) were also cleanly deprotected to (**8**) and (**10**) respectively but the application of this approach to *N*-sulfonyl carbamates, such as (**11**), proved unsuccessful and only recovered starting material was isolated (entry 6). The deprotection of more functionalised precursors such as (**12**), (**14**) and (**16**) was also possible (entries 7-9). It should be noted that the cinnamoyl group present in (**16**) was not reduced as would be expected if the reaction employed SmI_2 in the presence of a proton source or an additive solvent, such as HMPA.[3] Deprotection, without concomitant reduction, was also observed on reaction of the related amide (**18**) to produce (**19**) (entry 10).

Regioselective desulfonylation could also be achieved using a starting material containing a carbon-chlorine bond (scheme 2). Thus the serine-derived precursor (**20**) could be deprotected to afford the desired primary chloride (**21**) in 58% yield; the by-product dehydroamino acid (**22**), resulting from elimination of HCl, was isolated in only 14% yield.

Table.

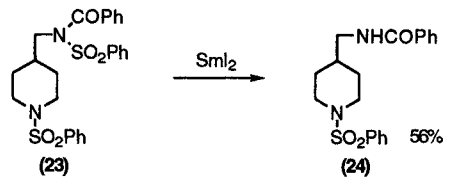
Entry	Sulfonamide	Product	Yield (%)
1	PhCON–Bn, Ts (3)	PhCON–Bn, H (2)	87
2	PhCON–Bn, SO_2Me (4)	PhCON–Bn, H (2)	71
3	*t*-BuCON–Bn, SO_2Ph (5)	*t*-BuCON–Bn, H (6)	57
4	 (7)	 (8)	88
5	 (9)	 (10)	62
6	BnO_2C–N–Bn, SO_2Ph (11)	Starting material	0
7	PhO_2S–NCOPh, Bn (12)	NHCOPh, Bn (13)	83
8	 (14)	 (15)	74
9	 (16)	 (17)	63
10	 (18)	 (19)	44



Scheme 2

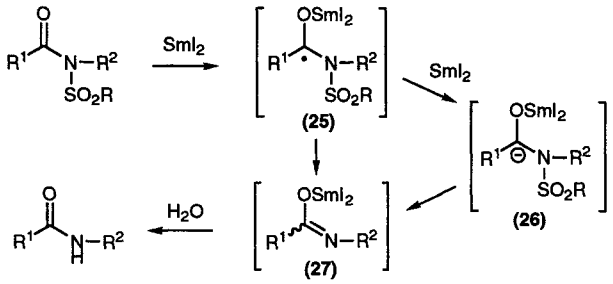
The mild reaction conditions employed in this deprotection method also allows the selective desulfonylation of an *N*-sulfonyl amide in the presence of an *N*-alkyl sulfonamide. As shown in scheme 3, the reaction of piperidine (**23**) with SmI_2 promotes selective N-S bond cleavage leading to the formation of the secondary amide (**24**) in 56% yield.

The mechanism for the deprotection reaction could involve electron transfer from SmI_2 to the sulfonyl group and related electron-transfer methods for sulfonamide deprotection are known.[2,13] Alternatively, electron-transfer to the amide carbonyl is possible to give the Sm(III)



Scheme 3

species (**25**) (scheme 4). This could undergo β-elimination of the sulfonyl radical (RSO_2•) giving (**26**) which upon aqueous work-up is expected to yield the deprotected amide. It is also possible that (**25**) undergoes further reduction (by SmI_2) to produce a carbanion (**26**) which subsequently eliminates the sulfonyl anion (RSO_2-) to produce (**27**).



Scheme 4

This simple deprotection method complements the known N-CO amide bond cleavage of these types of compound which occurs on treatment with base.[14] The compatibility of SmI_2 with a range of functional groups and the very mild reaction conditions employed make this method very attractive for application in synthesis.

Acknowledgements

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References and Notes

(1) For a recent review see Molander, G.A.; Harris, C.R. *Chem. Rev.* **1996**, *96*, 307.

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(7) For a related deprotection using tributyltin hydride (Bu_3SnH, AIBN, toluene, 110°C) see Parsons, A.F.; Pettifer, R.M. *Tetrahedron Lett.* **1996**, *37*, 1667.

(8) SmI_2 was purchased as a 0.1*M* solution in tetrahydrofuran from the Aldrich Chemical Company.

(9) *General experimental procedure*: To a solution of the *N*-acyl sulfonamide (0.17-0.32 mmol) in dry THF (3-4ml) was added SmI_2 (3 equiv., 0.1 *M* solution in THF) at 0°C under a N_2 atmosphere. The reaction mixture was stirred at 0°C for 10 minutes, allowed to warm to room temperature, and then quenched by the addition of saturated aqueous sodium bicarbonate (15ml). The aqueous phase was extracted with EtOAc (2 x 15ml) and the combined organic phase was then washed with brine (20ml), dried ($MgSO_4$), and evaporated *in vacuo* to afford crude product which was purified by column chromatography (silica). (The aqueous work-up was found not to be essential and in a few cases the reaction mixture was simply evaporated under reduced pressure to afford crude product).

(10) All new compounds exhibited satisfactory spectral and analytical (high resolution mass) data.

(11) Ogawa, A.; Takami, N.; Sekiguchi, M.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992**, *114*, 8729.

(12) Reaction of the corresponding *N*-acetyl derivative (under the same reaction conditions) was unsuccessful.

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