Deprotection of Arenesulfonamides with Samarium Iodide

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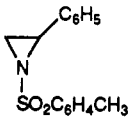
Summary: Deprotection of *N*-benzenesulfonamides or *N*-*p*-toluenesulfonamides to the parent primary or secondary amines (2,3-dialkylaziridines; α-amino acids) occurs in good yield upon heating with excess SmI_2 in THF/DMPU.

We report that *N*-(arylsulfonyl)amines can be deprotected efficiently using SmI_2 in a refluxing mixture of THF and DMPU (*N*,*N*'-dimethylpropyleneurea).[1] The procedure requires 6 mol of SmI_2 per mole of the sulfonamide or the presence of excess samarium metal to recycle Sm(III) salts[2] (see Table 1, entry 3). This is because the products of initial S–N cleavage are reduced more rapidly than is the starting *N*-(arylsulfonyl) derivative. A detailed accounting of the sulfur-containing byproducts has not been made, but diaryl disulfides and aryl mercaptans are consistently formed along with other derivatives containing the Ar–S fragment. Separation of the amine can be done by simple acid–base extraction, and the crude amines obtained in this way (>90% recovery) are contaminated only by traces of DMPU. Further purification by chromatography gives the isolated amines in good yield (Table 1).

By analogy to the well-known reductive cleavage of arylsulfonamides using Na/NH_3 or electrolysis, the mechanism for the SmI_2 reactions probably involves electron transfer to the sulfonyl group.[3,4] Mechanistically related photoinduced electron-transfer methods for sulfonamide deprotection are also known.[5] However, the detailed cleavage mechanism may be different for the SmI_2 technique, depending on whether the S–N cleavage process involves a one-electron or a two-electron pathway. The role of samarium salts is also not clear, and Lewis acid catalysis by Sm(III) is a possibility.

Deprotection of the *N*-(phenylsulfonyl) group was relatively fast compared to the *p*-toluenesulfonyl analogue (see entry 1 vs entry 2 and entry 7 vs entry 5, Table 1). Presumably, this difference reflects the increased electron affinity of the $C_6H_5SO_2$ substituent.[4b,c] The sulfonamides derived from primary and secondary amines were cleaved at about the same rate, suggesting little role for steric effects. Relatively fast cleavage was observed for the *N*-(toluenesulfonyl)aziridine derivatives (entries 9 and 10). Tentatively, the latter results are attributed to an increase in *s*-character expected for the exocyclic N–S bond in the strained ring. However, the qualitative rate differences are not large among any of the examples listed in the table, and all of these sulfonamides probably follow the same pathway for S–N cleavage.

One additional aziridine example was studied and gave strikingly different results. Thus, treatment of **9** [2-phenyl-1-(*p*-toluenesulfonyl)aziridine][6] under the usual conditions (reflux, THF–DMPU) resulted in a rapid reaction, but the deprotected 2-phenylaziridine could not be isolated. The aziridine was also not obtained when the experiment was repeated at room temperature, but this experiment did produce ca. 10% of styrene. Analogous reductive deoxygenation of epoxides to the alkenes by SmI_2 has been reported in the literature.[7] Finally, when the same experiment was done using <1 mol equiv of SmI_2 at room temperature, only starting material along with a small amount of styrene was obtained.



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The amino acid deprotections encountered varying degrees of racemization under the standard conditions (entries 5, 6, and 8). Best results with phenylalanine were obtained with the more reactive *N*-(phenylsulfonyl) derivative **5** (entry 7, 97% ee). In the optimized experiment, **5** was added slowly to excess SmI_2. In a similar experiment taken to partial conversion, starting **4** was recovered enantiomerically pure. Furthermore, prolonged heating did not cause a significant change in product ee, suggesting that an intermediate in the reductive cleavage may be subject to racemization. However, no decisive evidence is available regarding the origin of 1.5% racemization with phenylalanine and 5% racemization with phenylglycine. Retention of enantiomeric purity has previously been reported in the deprotection of *N*-(*p*-toluenesulfonyl)threonine using the Na/NH_3 method, and several simpler analogues have been deprotected without racemization using strongly acidic conditions.[8a] We are not aware of previous attempts to deprotect the more racemization-prone *N*-(arylsulfonyl)phenylglycine.

The aziridine examples of Table 1 are significant because there are relatively few methods reported for the depro-

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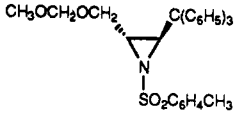
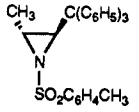
Table 1. Cleavage of Arenesulfonamides to Amines with SmI_2[a]

entry	sulfonamide	structure	time (h)	isolated yield (%) of amine
1	$C_6H_5SO_2N(CH_2C_6H_5)_2$	1	4.5	92[a]
2	$CH_3C_6H_4SO_2N(CH_2C_6H_5)_2$	2	8	84
3	$CH_3C_6H_4SO_2N(CH_2C_6H_5)_2$	2	8	50[b]
4	$CH_3C_6H_4SO_2NH(CH_2)_2C_6H_5$	3	5	72
5	$CH_3C_6H_4SO_2NHC(CH_2C_6H_5)HCO_2H$	4	11	58 (95% ee)[c]
6	$C_6H_5SO_2NHC(CH_2C_6H_5)HCO_2H$	5	6	63 (95% ee)[c]
7	$C_6H_5SO_2NHC(CH_2C_6H_5)HCO_2H$	5	1.5	70 (97% ee)[c,d]
8	$CH_3C_6H_4SO_2NHC(C_6H_5)HCO_2H$	6	9	60 (90% ee)[c]
9		7	3	88
10		8	4	97

[a] Typical procedure: 1 mmol of 1 + 60 mL of 0.1 M SmI_2/THF (preparation: ref 1i) + DMPU (4 mL). The mixture was refluxed under N_2, 92% yield (90% on 0.1 mmol scale) after chromatography on silica gel. The known arenesulfonamides were made from the amines as previously described (ref 11). [b] 2 mmol of **2**, 2 mmol of SmI_2 + 12 mmol of Sm(0); the reaction did not go to completion. A similar reaction on 0.1 mmol scale gave >90% yield. [c] The ee was determined by HPLC analysis of the 3,5-dinitrobenzoyl derivative on a Pirkle column (Regis, S-N1N-NAPHTHYLLEU). [d] The sulfonamide was added over 30 min to 9 equiv of SmI_2.

tection of aziridine derivatives.[9] Furthermore, the *N*-tosyl derivatives are now available with promising levels of enantioselectivity using $PhINSO_2C_6H_4CH_3$ in the presence of chiral catalysts.[10] The deprotection technique described here is restricted to alkyl-substituted *N*-(arenesulfonyl)-aziridines.

The *N*-(arylsulfonyl) group is a desirable protecting group for amine nitrogen because *N*-alkylarylsulfonamides are neutral, easily chromatographed, and often crystalline. On the other hand, removal of the arylsulfonyl group has been a recurring problem in the literature,[4c,9] probably because the available techniques are substrate dependent. Cleavage using SmI_2 also has substrate limitations as discussed above. However, compared to other electron-transfer methods, the SmI_2 technique has the advantage that no special apparatus is necessary. Issues of functional group compatibility are amply documented,[1] and the reaction conditions are sufficiently mild for use with the relatively difficult aziridine substrates.

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Supplementary Material Available: Experimental procedures for **2**, **5**, and **8** and characterization data and the ^1H NMR spectrum of **8** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be obtained from the ACS; see any current masthead page for ordering information.

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