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A Radical Approach to *N*-Desulfonylation

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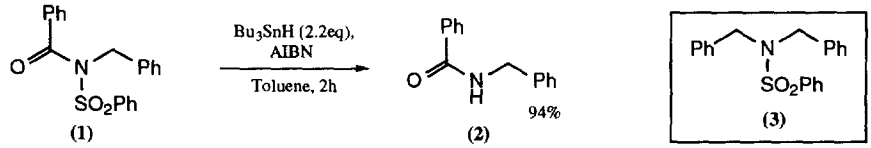
Abstract: The deprotection of *N*-sulfonylated amides can be achieved under neutral conditions by reaction with tributyltin hydride. Good yields are obtained using *N*-benzoyl and related amides while the corresponding *N*-acetyl derivatives are inert under the same reaction conditions. The mechanistic implications of this are discussed.

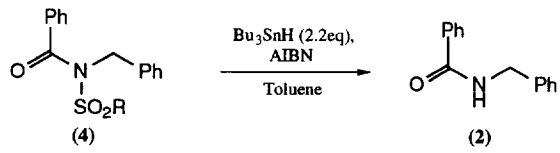
The preparation of *N*-sulfonamides constitutes a common method of amine protection in synthesis.[1] The resultant sulfonamides are often crystalline and more resistant to nucleophilic attack than carbamates. In addition, sulfonamides derived from primary amines can be readily deprotonated and the resultant anion can serve as a nucleophile for reaction with *eg.* alkyl or acyl halides.[2] Deprotection of the resulting *N*-alkyl or acyl sulfonamides produces secondary amines or amides respectively. However, sulfonamides are amongst the most stable of the nitrogen protecting groups and drastic deprotection conditions are required which often limit the scope of the procedures. Thus arylsulfonamides are cleaved by sodium in liquid ammonia,[3] sodium naphthalenide or anthracenide[4] and by heating to reflux in strong acid (*eg.* 48% HBr in the presence of phenol).[5] These harsh conditions have led to recent interest in the development of new deprotection methods which have included SmI_2[6,7] and electrolysis.[7] We now wish to report that the deprotection of *N*-acyl sulfonamides can be achieved under neutral reaction conditions using the radical generating agent Bu_3SnH.

As part of our research programme aimed at developing novel free radical reactions for use in synthesis, we became interested in the reaction of *N*-benzenesulfonamides such as (1)[8] with tributyltin hydride. Initial studies using 1.1 equivalents of Bu_3SnH in boiling benzene afforded 40% yield of the desired primary amide (2) formed on cleavage of the sulfonamide N-S bond (Scheme 1). This reaction was subsequently optimised to an excellent 94% yield using 2.2 equivalents of Bu_3SnH in boiling toluene. It is interesting to note that reaction of the corresponding amine (3) with tributyltin hydride did not lead to *N*-desulfonylation (under the same reaction conditions) and only starting material (3) was recovered.



Scheme 1

We then explored the deprotection of other *N*-benzoyl sulphonamides (**4**) as shown in Table 1. Thus reaction of the *N*-tosyl derivative (**4a**) led to clean sulfonamide deprotection to afford (**2**) in 83% yield after 2 hours. Reaction of the more sterically demanding dansyl derivative (**4b**) however, was found to be much slower and after 48 hours (**2**) was isolated in only 18% yield. We also investigated the deprotection of the alkylsulfonamides (**4c**) and (**4d**) and found that although deprotection of the camphor derivative (**4d**) was slow and inefficient (20% yield) the methylsulfonamide (**4c**) was deprotected in an excellent 71% yield. It should be emphasised that alkylsulfonamides are not normally used as protective groups in synthesis because of their stability.



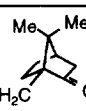
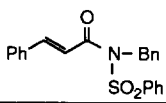
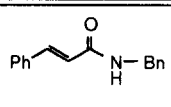
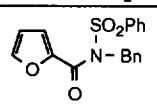
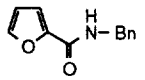
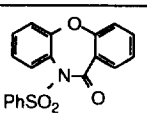
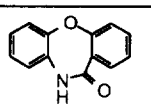
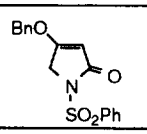
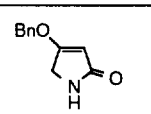
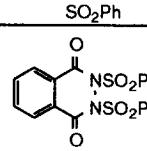
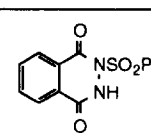
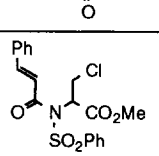
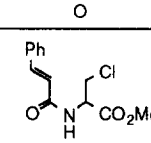
(4)	R	Yield of (2) (%)
a		83
b		18
c	Me	71
d		20

Table 1

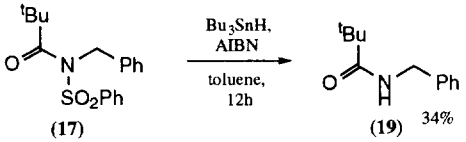
Sulfonamide	Product	Yield (%)
 (5)	 (11)	94
 (6)	 (12)	82
 (7)	 (13)	77
 (8)	 (14)	35 (79#)
 (9)	 (15)	59†
 (10)	 (16)	83*

Yield based on recovered starting material. †Prepared using 4.4 (rather than 2.2) equiv. of Bu_3SnH. *Prepared using 1.1 equiv. of Bu_3SnH.

Table 2

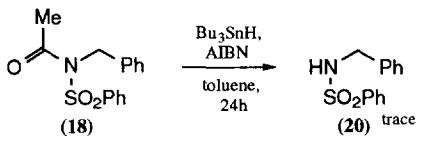
The phenylsulfonyl deprotection method was found to work on a variety of different substrates (**5**)-(**10**) as shown in Table 2. The cinnamoyl, furfuroyl and oxazepin-11-one sulfonamides (**5**)-(**7**) were cleanly deprotected to (**11**)-(**13**) in good to excellent yield after 1-3 hours while the pyrroline-2-one derivative (**8**) was found to be more resistant and a 35% yield of (**14**) was achieved after 48 hours. Monodeprotection of the phthalhydrazide derivative (**9**) could also be achieved even using an excess of Bu_3SnH (4.4 equivalents) to give (**15**) in 59% yield. Of particular note is the chemoselective deprotection of chloride (**10**) to form (**16**). Using 1.1 equivalents of Bu_3SnH led to exclusive deprotection of the amide; no reduction of the primary chloride was observed. The chemoselective nature of this deprotection method should allow application to highly functionalised substrates.

With a view to investigating the generality of this deprotection reaction, we prepared the pivaloyl and acetyl sulphonamides (**17**) and (**18**) (Schemes 2 and 3). We found that on treatment of (**17**) with tributyltin hydride, using the same reaction conditions as employed earlier for (**1**), the deprotection was considerably slower and proceeded to give (**19**) in only 34% yield after 12 hours. With the acetyl derivative (**18**) we observed no desulfonylation at all and after heating for 24 hours only a trace amount of the sulfonamide (**20**), resulting from amide bond cleavage, was isolated.[9]



(**17**) (**19**)

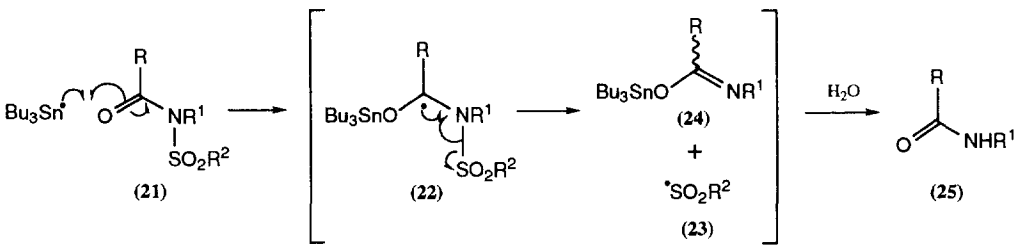
Scheme 2



(**18**) (**20**)

Scheme 3

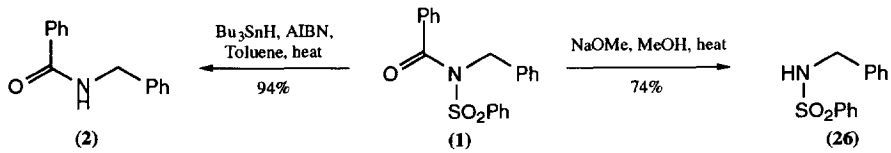
Clearly the nature of the amide substituent plays a key role in the deprotection reaction and one possible mechanism which could account for this is shown in Scheme 4. In this mechanism initial attack by the Bu_3Sn radical occurs at the amide bond of (**21**) and addition is expected to be facilitated if the amide substituent R is able to stabilise the resultant tertiary radical (**22**). β-Elimination of the sulphonyl radical (**23**) would then afford (**24**) which upon aqueous work-up is expected to yield the deprotected amide (**25**).[10,11] However, an alternative electron transfer mechanism[12] cannot be excluded and further work is needed to elucidate the reaction mechanism.



Scheme 4

We feel that this novel deprotection method could find application in synthesis because of the mild reaction conditions employed. This method also complements the known[13] N-CO amide cleavage of these types of compound which occurs on treatment with base. Thus, for example, we found that on treatment of (**1**) with sodium methoxide, the sulfonamide (**26**) was isolated in 74% yield (Scheme 5). In addition these results

could promote interest in the reaction of radicals with amides which to our knowledge has been unexplored; we are currently investigating further applications of this chemistry.



Scheme 5

Typical Procedure

Deprotection of (1): A solution of (1) (200mg, 0.57mmol) in degassed toluene (20ml) was heated to reflux and Bu_3SnH (365mg, 1.25mmol) and AIBN (18mg, 0.11mmol) were added in one portion as a solution in toluene (5ml) under an nitrogen atmosphere. 0.1 Equivalents of AIBN was added portionwise every 0.5h until the reaction had gone to completion (2h) as indicated by TLC analysis. The toluene was then removed *in vacuo* and diethyl ether (20ml) and aqueous potassium fluoride (8%, 20ml) were added to the residue and the mixture stirred for 2h. The organic layer was separated, washed with water and brine, dried ($MgSO_4$) and evaporated under reduced pressure to afford crude product which was purified by column chromatography (petrol:ethyl acetate, 2:1; silica) to afford (2) (113mg, 94%) as a white solid; m.p. 104-105°C (lit.[14] 106-107°C).

Acknowledgements

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