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A New Method for Deprotection of Benzothiazolesulfonamides Using a Thiol and Base.

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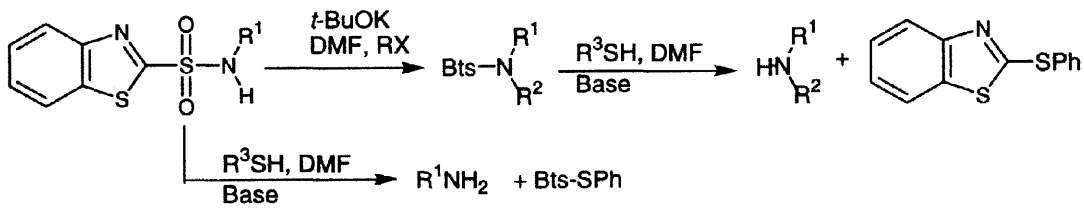
Abstract: Benzothiazolesulfonamides of primary and secondary amines are efficiently cleaved by a nucleophilic aromatic substitution with a thiol and a base such as potassium *t*-butoxide or diisopropylethyl amine in DMF. © 1998 Elsevier Science Ltd. All rights reserved.

The chemistry of protective groups continues to be an active area of research. Although there are hundreds of protective groups that can be introduced and removed by a variety of methods,[1] new and milder methods continue to be developed for both the introduction and cleavage of many of the existing protective groups. The availability of a diverse set of orthogonal methods for protective group cleavage is of considerable importance in the design and execution of a synthesis. We thus wish to report our preliminary results on a new non acidic method for the cleavage of benzothiazolesulfonamides,[2,3] recently introduced by Vedejs for nitrogen protection of amino acids.[4] Currently the most convenient methodology for Bts cleavage is a reductive one using either Zn/AcOH, Al(Hg) or hot hypophosphorous acid. We have found a new process for deprotection of Bts-protected amines that proceeds by nucleophilic aromatic substitution at the 2-position of the Bts group with thiophenol and base to give the free amine and 2-phenylthiobenzothiazole.



In order to examine the effectiveness of the new cleavage process, a number of derivatives were prepared either by direct sulfonylation of the amine or by alkylation of a primary Bts derivative in analogy to Fukuyama's recent work using the nosylate.[5] The cleavage reaction is not limited to the use of thiophenol. Other less malodorous thiols such as dithiothreitol (Entry 5) are also effective. The results to date are presented in Table I. Entry 6 illustrates that the method is mild and can be used in such complex environments as Taxol®. Although it might be expected that sulfonamides of primary amines may not cleave as easily as the secondary derivatives because of the acidic proton, this proved not to be a problem.

In conclusion we have shown that benzothiazolesulfonamides are cleaved under very mildly basic conditions with thiolate which complements the reductive and acidic conditions developed by Vedejs.

Representative Cleavage Procedure: To a solution of thiophenol (0.56 g, 5.06 mmol), potassium *tert*-butoxide (2.58 mL of 1.97*M* in THF) in 5 mL DMF at rt was added *N*, *N*-dibenzyl-1,3-Bt-2-sulfonamide (1 g,

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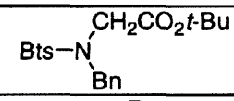
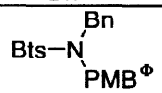
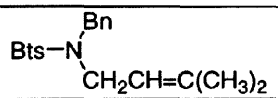
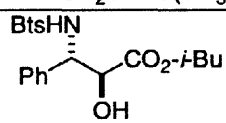
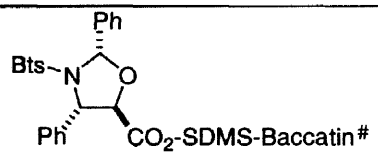
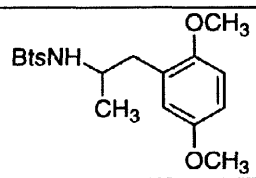
2.53 mmol). When TLC showed complete reaction the mixture was acidified with aq. 10% HCl. The aqueous layer was washed with EtOAc to remove the thioether and residual PhSH and then made basic with NaOH. The amine was extracted with EtOAc, washed with H_2O and the EtOAc solution dried over magnesium sulfate. Filtration and concentration gave 470 mg (92% yield) of the amine which was 98.3% pure by GC. IR 3328, 1450cm^{-1}; ^{1}H NMR: δ(ppm) 7.29 (m, 10 H), 3.81 (s, 4 H), 1.62 (s, N, 1 H); ^{13}C NMR: δ(ppm) 140.37, 128.40, 128.28, 128.16, 126.95, 53.19.

Table I: Cleavage of benzothiazolesulfonamides with thiolate.

Entry	Sulfonamide[6]	Conditions	% Yield of Amine
1		PhSH, t-BuOK, DMF	92
2		PhSH, t-BuOK, DMF	82
3		PhSH, t-BuOK, DMF	75
4		PhSH, t-BuOK, DMF	71
5		PhSH, DIPEA, DMF DTT$^{\Omega}$, DIPEA, DMF	71 62
6		PhSH, DIPEA, DMF	78
7		PhSH, DIPEA, DMF	91

Φ) PMB = 4-methoxybenzyl, #) SDMS = siamyldimethylsilyl, Ω) DTT = dithiothreitol

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6. All new compounds gave satisfactory IR, ^{13}C NMR, ^{1}H NMR and CHN or high resolution MS analyses.