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A Cautionary Note on the Use of *p*-Nitrobenzenesulfonamides as Protecting Groups

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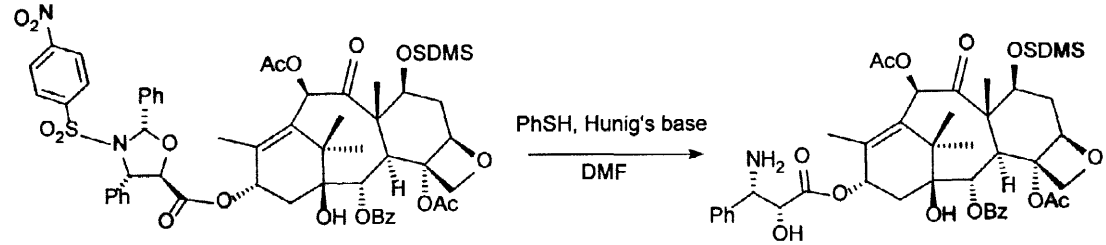
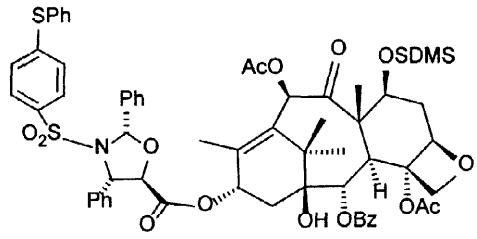
Abstract: The cleavage of *p*-nitrobenzenesulfonamides using thiolate was found to give poor regioselectivity. Cleavage requires addition of thiolate at the sulfonamide carbon, but some addition occurs at the nitro carbon resulting in simple displacement of the nitro group rather than sulfonamide cleavage. The side reaction is most prevalent with cyclic amines and steric effects play only a limited role. This lack of regioselectivity is not observed for *o*-nitrobenzenesulfonamides. © 1998 Elsevier Science Ltd. All rights reserved.

Recently Fukuyama described the use of thiolate for the cleavage of *p*-nitrobenzenesulfonamides of secondary amines, a deprotection process which has considerable potential in synthesis.[1] Because of some of the advantages of the sulfonamide group we examined its use in a synthesis and found that the addition of thiolate to form the intermediate Meisenheimer complex is not completely regioselective.

As part of a program in Taxol™ chemistry we prepared and evaluated the cleavage of the nosylate from the oxazolidine **1** and were surprised to find that a considerable amount (9% yield) of thiolate addition occured at the carbon bearing the nitro group to give the thioether **3** rather than at the expected sulfonamide carbon to give the deprotected amino alcohol **2**. This, of course, is quite detrimental for the use of the *p*-nosylate as a protecting group since it is now impossible to cleave the resulting 4-phenylthioether derivative.



1 **2**



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These results led us to explore the possible reasons for this previously unreported regioselectivity. Is it a steric effect or electronic effect which directs thiolate addition to the nitro bearing carbon of the sulfonamide? Table I gives the results for the cleavage of a number of *p*-nitrobenzenesulfonamides of varying acidity and steric

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demand. Clearly the acidity of the amine is not an overriding factor in determining selectivity because dibenzyl amine and morpholine which have similar pKa's but different steric requirements, show a large difference in the regioselectivity of thiolate addition. The cyclic and sterically similar pyrrolidine and morpholine derivatives **4d** and **4e** give substantially more addition at the nitro carbon than any of the acyclic sulfonamides. One would also expect that a large steric requirement would tend to direct thiolate addition to the nitro carbon which is not consistent with the results for the diisopropyl amine derivative **4a** which gives only 3.9% (isolated) of the phenyl thioether and the sterically less demanding pyrrolidine sulfonamide **4d** which shows nearly double the amount of addition at the nitro carbon. From these results it is not clear what is responsible for the regioselectivity of thiolate addition. The general observation is that sulfonamides of cyclic amines are more prone to give additon at the nitro carbon than are those derived from acyclic amines. Fortunately, in contrast to the para derivative, when the ortho nosylate of morpholine was treated with thiolate no evidence could be found for the addition of thiolate to the nitro carbon. Only the desired cleavage product is observered.

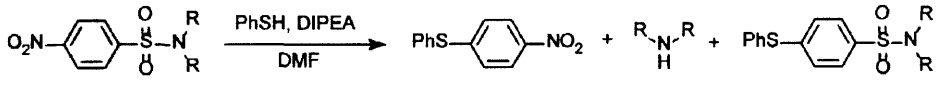

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Table I: Percent of thiolate addition to the nitro carbon of ortho and para nosylates.

	Diisopropyl *p*-nosylate (a)	Methylbenzy *p*-nosylate (b)	Dibenzyl *p*-nosylate (c)	Pyrrolidine *p*-nosylate (d)	Morpholine *p*-nosylate (e)	Morpholine *o*-nosylate (f)
% Addition at nitro carbon (isolated)[2]	3.9[Φ Ω φ]	3.7	3.6	7.2	19.3	none found
% Addition at nitro carbon (by HPLC)	6.1	7.5	8.3 (3.4)[&]	13.7	34.5 (27.8)[#]	none found
pKa of conj. acid	11.1	9.5	8.5[3]	11.3	8.3	

(φ) All reactions proceeded to >97% completion. (Ω) Unless otherwise noted, PhSH. DIPEA, DMF at rt was used to effect cleavage. (&) Deprotection with PhSH, *t*-BuOK, DMF, -20°C. (#) Deprotection with K_2CO_3, PhSH, DMF, rt. (Φ) Clean separation could not be obtained by chromatography.

In conclusion we have found that thiolate cleavage of the *p*-nitrobenzenesulfonamides may not be completely selective, especially with certain amine derivatives, and thus some care must be taken when planning to use this group for amine protection. On the other hand, this does not appear to be a problem with the *o*-nitrobenzenesulfonamide.

References

1. Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* (1995) *36*, 6373.

2. All new compounds gave satisfactory NMR, IR and high resolution Mass Spectral data.

3. Christensen, J.J., Izatt, R. M., Wrathall D. P., Hansen, L. D., *J. Chem. Soc. (A)*, (1969) 1212