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A study of the functional group compatibility of sulfoximination methods

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Abstract—The sulfoximination of a range of sulfoxides possessing functionalised side-chains using mesitylene sulfonyl hydroxylamine or iminoiodane reagents is discussed. The use of iminoiodane reagents possessing removable protecting groups (*p*-nosyl and Ses) is reported along with conditions for the deprotection of the sulfoximine adducts.

1. Introduction

During the course of our research into compounds possessing the sulfoximine functional group we have had cause to prepare a number of compounds which also contain other functionalities such as alkenes, alcohols, esters and carbamates. Of the methods available for the introduction of the sulfoximine group[1] the simplest is the imination of the corresponding sulfoxide either using mesitylene sulfonyl hydroxylamine (MSH)[2,3] or using iminoiodane reagents such as Ph-I=NTs[4] under Cu(I)-catalysed conditions. Herein we report our findings regarding the functional group compatibility of MSH and the iminoiodane reagent Ph–I=N–Ts along with use of modified iminoiodane reagents Ph–I=N–Ns[5] (Ns = *para*-nitrophenyl sulfonyl) and Ph–I=N–Ses[6] (Ses = trimethylsilylethyl sulfonyl) possessing removable protecting groups.

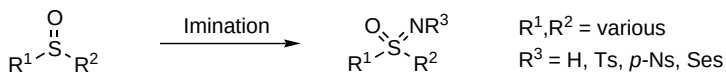
2. Results and discussion

The results obtained for the reaction of a range of sulfoxides **1a**–**h** under differing imination conditions are summarised in Scheme 1 and Table 1. To date the modified iminoiodane reagent Ph–I=N–Ns has seen limited use in sulfoximine synthesis[5] and Ph–I=N–Ses has only been employed in aziridination chemistry.[6] The results presented here clearly show that these reagents are quite generally applicable to sulfoximine synthesis.

In general the iminoiodane reagents appear to be more versatile than MSH, which fails to react with the vinylic sulfoxide **1b** and the β-bromo sulfoxide **1d**, and gives very poor conversion of the β-sulfinyl propionate **1f** and *S*-methyl cysteine derivative **1h** (in both of these cases a competing lactamisation of the free sulfoximine is observed[7]). Surprisingly MSH and all three iminoiodane reagents tolerate the presence of a free hydroxyl group in sulfoxide **1c** giving good to moderate yields of the corresponding sulfoximines in all cases.

One substrate which could not be iminated by any of the methods investigated was the α-sulfinyl ethanoate **1e**. This lack of reactivity is probably due to the inductive electron withdrawing effect of the ester group making the lone pair on sulfur much less nucleophilic than in the other substrates. However, this sulfoximine derivative can be prepared by introduction of the ester group after imination of phenyl methyl sulfoxide **1a**.[8]

Our ultimate synthetic goal was to produce sulfoximines possessing side-chain functionalities which could also be derivatised at nitrogen. In order to achieve this



Scheme 1.

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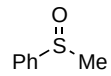
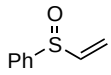
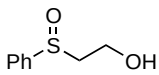
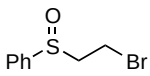
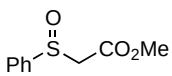
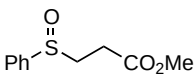
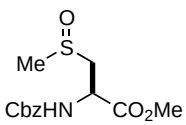
Table 1.

Substrate		Yield (%) of Sulfoximine Using Specified Reagent			
		MSH[a]	Ph-I=N-Ts[b]	Ph-I=N-Ns[b]	Ph-I=N-Ses[b]
1a		75	59	69	68
1b		0	93	65	30[c]
1c		95	90	40	59
1d		0	41	-	-
1e		0	0	0	0
1f		4[d]	78	55	50
1h		-	70[e]	48[e]	-

a) MSH (2 eq.), DCM, rt. then Na_2CO_3 (aq).

b) Iminoiodane (1.1 eq.), $CuPF_6$ (0.05eq), CH_3CN, 0°C- rt.

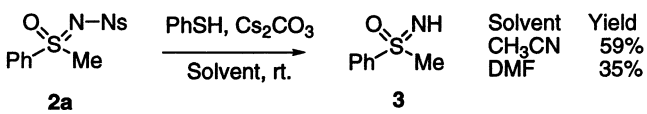
c) Unoptimised yield.

d) Cyclisation to form a lactam derivative was a major side reaction. A similar problem has been observed in the reaction of methyl cysteine derivatives with MSH (see reference 7).

e) A single diastereoisomer of sulfoxide was used, however, the configuration at sulfur is unknown.

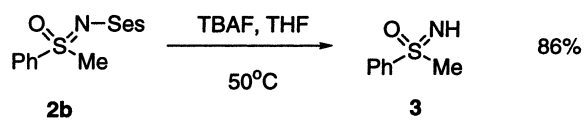
the use of MSH (giving free sulfoximines directly) or in the cases where MSH performed poorly, iminoiodanes with removable protecting groups, Ph–I=N–Ns and Ph–I=N–Ses, would be required. To the best of our knowledge methods for the removal of *p*-nosyl and Ses groups from the corresponding protected sulfoximines have not been previously reported. In our hands the *p*-nosyl group could be removed from the phenyl methyl sulfoximine **2a** using Cs_2CO_3, PhSH in either acetonitrile or DMF in 59 and 35% yields, respectively (Scheme 2). However, this reaction did not proceed cleanly with other functionalised sulfoximines such as those derived from **1b**, **1f** and **1h**.

Removal of the Ses group from phenyl methyl sulfoximine **2b** proceeded smoothly using TBAF in THF at 50°C giving the free sulfoximine **3** in 86% yield (Scheme 3). Investigations into the compatibility of this method with other functional groups is ongoing.



2a **3**

Scheme 2.



2b **3**

Scheme 3.

3. Conclusion

The use of iminoiodane reagents for the sulfoximination of a range of functionalised sulfoxides proceeds in moderate to good yield. Iminoidoanes are generally compatible with a wider range of functionality than MSH. The subsequent removal of *N*-protecting groups from the sulfoximine adducts is limited when the *p*-nosyl group is used but has potential to be more generally applicable in the case of the Ses group. This opens the way to the synthesis of highly functionalised sulfoximine-containing compounds.

4. Experimental

Example procedure for imination of 1f using Ph–I=N–Ses: Sulfoxide **1f** (1.0 equiv.) was dissolved in dry acetonitrile and $CuPF_6[CH_3CN]_4$ (0.05 equiv.) was added under an inert atmosphere (N_2). The mixture was cooled to 0°C and Ph–I=N–Ses (1.1 equiv.) was added portionwise. The mixture was allowed to warm to rt and stirred for a further 48 h. The solvent was evaporated and the residue dissolved in ethyl acetate and filtered through a silica plug. The product sulfoximine was then isolated as a waxy solid (50%) by recrystallisation from ethyl acetate/hexane mixture. δ_H (300 MHz, $CDCl_3$) 0.0 (9H, s, TMS), 1.1 (2H, m, CH_2), 2.8 (2H, m, CH_2), 3.1 (2H, m, CH_2), 3.6 (3H, s, CH_3), 4.85 (2H, m, CH_2), 7.6–8.0 (5H, m, ArH); δ_C (75 MHz, $CDCl_3$) −1.8 (TMS), 10.4 (CH_2), 27.9 (CH_2), 52.5 (CH_3), 53.5 (CH_2), 53.8 (CH_2), 128.5 (Ar), 129.8 (Ar), 134.8 (Ar), 136.1 (q, Ar), 169.7 (C=O); *m*/*z* (ES) 414.0 ($[M+Na]^+$, 100%); HRMS calcd for $C_{15}H_{25}NO_5S_2SiNa$ (414.0841), Found (414.0826).

Example procedure for removal of the Ses group from 2b: Sulfoximine **2b** (0.63 mmol), was dissolved in THF (10 ml) under an inert atmosphere (N_2) and TBAF (1.58 mmol, 1 M solution in THF) was added at rt. The mixture was then heated to 50°C for 72 h. The reaction mixture was concentrated and the crude product purified by column chromatography on silica eluted with ethyl acetate to give sulfoximine **3** as a colourless oil (88%). δ_H (300 MHz, $CDCl_3$) 2.67 (1H, s), 3.11 (3H, s), 7.51–7.68 (3H, m), 7.98–8.06 (2H, m).

Acknowledgements

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References

1. Reggelin, M.; Zur, C. *Synthesis* **2000**, 1.
2. Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1.
3. Johnson, C. R.; Kirchoff, R. A.; Corkins, H. G. *J. Org. Chem.* **1974**, *39*, 2458.
4. Muller, J. F. K.; Vogt, P. *Tetrahedron Lett.* **1998**, *39*, 4805.
5. Bolm, C.; Muniz, K.; Aguilar, N.; Kesselgruber, M.; Raabe, G. *Synthesis* **1999**, 1251.
6. Dauban, P.; Dodd, R. H. *J. Org. Chem.* **1999**, *64*, 5304.
7. Levenson, C. H.; Meyer, R. B., Jr. *J. Med. Chem.* **1984**, *27*, 228.
8. Bolm, C.; Moll, G.; Kahmann, J. D. *Chem. Eur. J.* **2001**, *7*, 1118.