Published in final edited form as:

Tetrahedron Lett. 2007 August 13; 48(33): 5771–5775. doi:10.1016/j.tetlet.2007.06.088.

Oxidative reactions of tetrahydrobenzimidazole derivatives with *N*-sulfonyloxaziridines

Rasapalli Sivappa, Panduka Koswatta, and Carl J. Lovely*

Department of Chemistry and Biochemistry, The University of Texas at Arlington, Arlington, TX 76019

Abstract

An investigation of the utility of *N*-sulfonyloxaziridines to effect the oxidative rearrangement of tetrahydrobenzimidazoles to spiro fused 5-imidazolones is reported. In addition to the anticipated rearrangement manifold, it was found that 2-amino substituted derivatives afford products resulting from rearrangement, or alternatively from addition of methanol or water depending on the nature of the *N*-substituents and reaction conditions.

As part of a broader investigation of the chemistry of imidazoles,¹ we recently reported a novel rearrangement reaction of tetrahydrobenzimidazoles (THB's, **1**) leading to the formation of spiro fused 5-imidazolones **2** upon treatment with dimethyldioxirane (DMDO, **1**→**2**, Scheme 1).^{2,3,4,5} While no detailed mechanistic studies were conducted, the reaction was formulated as proceeding via epoxide **3** in analogy with the corresponding rearrangement of *N*-acyl indoles with DMDO.^{6,7} Subsequent ring opening of intermediate **3** leads to the formation of the more stable zwitterion **4**, which rearranges *via* a pinacol-type process to provide **2**. While this chemistry was quite satisfactory in most respects, there were practical aspects of this reaction that rendered it somewhat inconvenient, particularly for small scale scouting experiments. Chief among the deficiencies was the need to prepare isolated DMDO solutions, which often were of variable concentration and would contain trace (and variable) amounts of water. Therefore, we sought to identify alternative oxidants that would effect this rearrangement. Among several possibilities, Davis' reagents, *N*-sulfonyloxaziridines,^{8,9} attracted our attention as they share many common characteristics with dioxiranes, therefore it occurred to us that this class of reagent may offer a shelf-stable alternative to DMDO. These reagents are readily accessible by oxidation of the *N*-sulfonylimine, which in turn can be obtained from condensation of the corresponding benzaldehyde derivative and a sulfonamide.¹⁰

In our previously reported studies,² it was found that the THB **1** needed to be reasonably electron rich for this reaction to occur, and so in preliminary experiments, the Me-substituted THB **1a** was employed. After a few test reactions, we were delighted to find that exposure of **1a** to 2.0 equivalents of the phenyl sulfonyloxaziridine **5** in CHCl₃ led to a smooth rearrangement reaction,¹¹ providing the spiro fused 5-imidazolone **2a** in 82% yield (entry 1, Table 1). Interestingly, in addition to the major rearrangement product, a small amount of a second product was isolated in ~ 2% yield. It was clear from the NMR data and HRMS analysis that this byproduct contained fragments derived from the oxaziridine. A clue to the identity of

* Corresponding author. Tel.: 817-272-5446; fax: 817-272-3808; e-mail: lovely@uta.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

the this product was found in a study by Dmitrienko of the utility of *N*-sulfonyloxaziridines as oxygen transfer agents with indoles.^{9,12} Instead of the desired oxindoles, formal [3+2] oxaziridine-alkene cycloadducts (across the indole 2,3-bond) were isolated as the major products (diastereomeric mixture) when simple benzaldehyde-derived oxaziridines were used.^{12,13} A similar adduct **8a** is formed in this case through net addition of the oxaziridine across the imidazole 4,5-bond. Although the relative stereochemistry of the benzylic center awaits assignment, the regiochemistry of the adduct has been proposed based on the putative mechanism of formation (Scheme 2). The isolation of **8a** has implications for the mechanism of this rearrangement reaction. As described above in Scheme 1, the DMDO-mediated rearrangement was proposed to proceed via the 3a,7a-epoxide **3**, which opens to the form **4**, and then rearranges.² The isolation of **8a** when an *N*-sulfonyloxaziridine is employed suggests an alternative mechanistic pathway involving the direct formation of zwitterion **5**, and then either elimination of the imine and rearrangement to the spiro imidazolone (**7**→**2**; Scheme 2), or intramolecular trapping to generate **8** (**7**→**8**, Scheme 2). While extrapolation of this mechanistic proposal to the DMDO-mediated process should be made with caution, the direct formation of the zwitterionic intermediate **4** (or the corresponding DMDO adduct related to **7**) cannot be ruled out on the basis of the experimental data available.⁶

Given the success of this initial reaction we began to investigate the scope and limitations of this reaction. In the course of our earlier DMDO study,² we had assembled a collection of THB derivatives that differed in the nature of the *N*-substituent **1a-e** and the C2 substituent **1f**. These were investigated in the rearrangement chemistry with Davis' reagents (Ar = Ph, **5** or Ar = *p*-NO₂C₆H₄, **6**) and the outcome of this investigation is reported in Table 1 (entries 2-6).¹⁴ As can be seen, the rearrangement proceeds with the same types of substrates that undergo reaction with DMDO, and similarly, the same set of unreactive substrates fail to rearrange, including the DMAS-protected (DMAS = Me₂NSO₂) derivative **1e**. For the more electron deficient substrates, heating was required to effect rearrangement (**1c**, entry 3, Table 1), and in some cases the more reactive oxaziridine (Ar = 4-NO₂C₆H₄, **6**) was required (**1e**, entry 6, Table 1). We also investigated the reaction of unsubstituted tetrahydrobenzimidazole, i.e., PG = H and found that it reacts with both Davis' reagents (Ar = Ph or Ar = 4-NO₂C₆H₄), but provides the addition product **9a** or **9b** as a separable mixture of as yet unassigned diastereomers, rather than rearrangement products.

One major deficiency of the DMDO-mediated rearrangements was application of this reaction to 2-amino substituted derivatives.¹⁵ It was our intention to use this transformation in approaches to a variety of marine natural products in the oroidin and related families.^{1,15,16} Therefore, we decided to investigate the use of Davis' reagents with substrates of this type. Since Davis' reagent led to rearrangement of the benzyl-protected THB and as some of our ongoing total synthesis efforts utilized benzyl-protected derivatives, we prepared both the 2-azido, and the *N*-phthalimidoyl derivatives **10** and **14** respectively for investigation. The 2-azido derivative **10** was obtained by lithiation of **1b** at C2, followed by treatment with TsN₃. NaBH₄ reduction of **10** and treatment **12** with the modified Nefkens' reagent provided the phthalimide derivative **14**.¹⁷ We had found in our initial studies with Davis' reagent that the DMAS-protected THB **1e** did not undergo rearrangement, but we speculated that if the electron density of the imidazole moiety could be increased, a rearrangement might ensue. Accordingly, the 2-amino derivative **15** was prepared as above via metalation and trapping with TsN₃ providing the 2-azido congener **11** (Scheme 3), which was easily reduced to the amine **13**, which in turn was protected with a phthaloyl moiety on treatment with Nefkens' reagent, providing **15** (Scheme 3).

Gratifyingly, on treatment of the benzyl-protected derivatives with the nitrophenyl substituted oxaziridine **6**, both **10** and **14** underwent smooth rearrangement to the corresponding 5-imidazolones **16** and **17** respectively (entries 1 and 2, Table 2). Unfortunately, this was no the

case with the DMAS derivatives as neither the protected substrate **15** nor the azide **11** rearranged (entries 4 and 5, Table 2), however, we discovered that when the 2-amino derivative **13** was reacted with the oxaziridine **6** in methanol a rapid reaction occurred, but not the anticipated rearrangement to a 5-imidazolone.¹⁸ On isolation of the product it was clear from the NMR data that it contained a methoxy group, and the typical signal due to a carbonyl in the ¹³C NMR spectrum at around $\delta_C = 180$ ppm was absent.² The NMR and MS data pointed to the formation of the hydroxy methyl ether **21** (Scheme 5), in which the stereochemistry was assigned on the basis of the methanol trapping the (incipient) carbocation on the opposite face from the oxaziridine approach.¹⁹ Subsequently, an X-ray structure determination proved that both our stereochemical proposal and our constitutional assignment were incorrect. The methoxy and hydroxy groups were in fact *cis* to one another and there was a net migration of the DMAS moiety to the exocyclic nitrogen. Presumably, the locus of the N-protecting group changes as a result of a ring opening/reclosure sequence via **24** depicted in Scheme 5. We cannot distinguish at this time whether the initial formation of the expected adduct **21** occurs, and that this rearranges to form the observed adduct **19**, or the formation of the *cis* isomer **23** occurs, which then rearranges to **19**. It was also found that a similar reaction could be performed in aqueous acetone, leading to a dihydroxylation product (**20**, entry 7, Table 2). The constitution was assigned on the basis of the ¹³C NMR spectrum, in which only five unique carbon signals were observed. The stereochemical assignment is by analogy to **19**.²⁰ As the DMAS-derivative **15** underwent an addition reaction, we wanted to establish whether the Bn-derivative **12** also underwent this same type of transformation. Interestingly, and in contrast, subjection of **12** to the same reaction conditions led to rearrangement, rather than addition, providing the imidazolone **16** (entry 3, Table 2).

This spectrum of reactivity is interesting and presumably reflects the relative stabilities of the zwitterionic intermediate **5**. In the case of **12**, this is highly electron rich and so the carbocationic center is quite stable (via delocalization of the amine lone pair), which in turn permits collapse of the carbinolamine (with expulsion of the imine) and rearrangement. On the other hand, with the more electron deficient system **13**, presumably the zwitterion **19** is relatively unstable, and is heavily solvated leading to trapping of the carbocation with methanol.

In summary, aryl *N*-sulfonyloxaziridines are effective reagents for the oxidative rearrangement of tetrahydrobenzimidazoles to the corresponding spiro fused 5-imidazolones or in some cases to bis addition products. Although we are still investigating this chemistry, there are some fairly subtle effects in play here that lead to various outcomes depending on the nature of the 2-substituent and the solvent employed. Also of note is the fact that a free amine can be tolerated with these substrates leading to either rearrangement or addition of solvent depending upon the N1 protecting group. These reagents provide a shelf stable alternative to DMDO, which has to be prepared in isolated form to effect this rearrangement.² We are continuing to explore the utility of Davis' reagent to effect oxidation reactions of imidazole-containing substrates and its use in total synthesis efforts.

Acknowledgments

Prof. H. V. Rasika Dias is gratefully acknowledged for obtaining and solving the X-ray structure of compound **19**. This work was supported by the Robert A. Welch Foundation (Y-1362) and the NIH (GM065503). The NSF (CHE-9601771, CHE-0234811) is thanked for partial funding of the purchases of the NMR spectrometers used in this work.

References

1. He Y, Du H, Sivappa R, Lovely CJ. Synlett 2006:965.
2. Lovely CJ, Du H, He Y, Dias HVR. Org Lett 2004;6:735. [PubMed: 14986962]

3. A similar type of rearrangement occurs on treatment of tetrahydrobenzimidazoles with singlet oxygen in the presence of base. See (a) Bernhart CA, Perreaut PM, Ferrari BP, Muneaux YA, Assens JLA, Clement J, Haudricourt F, Muneaux CF, Taillades JE, Vignal MA, Gougat J, Guiraudou PR, Lacour CA, Roccon A, Cazaubon CF, Breliere JC, Le Fur G, Nisato N. *J Med Chem* 1993;36:3371. [PubMed: 8230127] (b) Kimura M, Lu G, Iga H, Tsunenaga M, Zhang Z, Hu Z. *Tetrahedron Lett* 2007;48:3109.
4. The Chen lab has reported a similar oxidative rearrangement of imidazolones using MCPBA. See Tan X, Chen C. *Angew Chem, Int Ed* 2006;45:4345.
5. Romo and co-workers have reported several examples of reactions of imidazolones with DMDO, however these rearrange via an alternate pathway providing allylic alcohols, which on treatment with NCS rearrange to spiro imidazolones. See (a) Dilley AS, Romo D. *Org Lett* 2001;3:1535. [PubMed: 11388860] (b) Dransfield PJ, Wang S, Dilley A, Romo D. *Org Lett* 2005;7:1679. [PubMed: 15844879] (c) Dransfield PJ, Dilley AS, Wang S, Romo D. *Tetrahedron* 2006;62:5223. (d) Wang S, Dilley AS, Poullennec KG, Romo D. *Tetrahedron* 2006;62:7155.
6. (a) Zhang X, Foote CS. *J Am Chem Soc* 1993;115:8867. (b) Adam W, Ahrweiler M, Sauter M, Schmiedeskamp B. *Tetrahedron Lett* 1993;34:5247.
7. For DMDO oxidation of simple enamines in which the epoxide was observed and characterized see (a) Adam W, Reinhardt D, Reissig HU, Paulini K. *Tetrahedron* 1995;51:12257. (b) Burgess LE, Gross EKM, Jurka J. *Tetrahedron Lett* 1996;37:3255. Also see (c) Lavilla R, Barón X, Coll O, Gullón F, Masdeu C, Bosch J. *J Org Chem* 1998;63:10001.
8. Davis, F.A.; Scheppard, A.C. 1989, 45, 5703.
9. While this manuscript was in preparation, the Williams lab reported that *N*-sulfonyloxaziridines can be utilized in the oxidative rearrangement of indoles to spiro oxindoles. See (a) Grubbs AW, Artman GD III, Tsukamoto S, Williams RM. *Angew Chem Int Ed* 2007;46:2257. (b) Greshock TJ, Grubbs AW, Tsukamoto S, Williams RM. *Angew Chem Int Ed* 2007;46:2262. (c) Greshock TJ, Grubbs AW, Williams RM. *Tetrahedron* 2007;63:6124. [PubMed: 18596842]
10. (a) Jennings WB, Lovely CJ. *Tetrahedron Lett* 1988;29:3725. (b) Jennings WB, Lovely CJ. *Tetrahedron* 1991;47:5561.
11. Other solvents were investigated including CH₂Cl₂, MeCN, PhH and MeOH, but CHCl₃ was generally superior.
12. Mithani S, Drew DM, Rydberg EH, Taylor NJ, Mooibroek S, Dmitrienko GI. *J Am Chem Soc* 1997;119:1159. See also ref. 9.
13. It has recently been demonstrated that *N*-sulfonyloxaziridines undergo a [3+2] cycloaddition reaction with olefins in the presence of CuX, see Michaelis DJ, Shaffer CJ, Yoon TP. *J Am Chem Soc* 2007;129:1866. [PubMed: 17260993]
14. The [3+2] adduct **6b** was obtained with **1b**, but we were unable to fully purify this material to determine an accurate yield, but it was of the same order as **1a**.
15. He, Y. Ph.D. Dissertation, **2004**, The University of Texas at Arlington.
16. (a) Hoffmann H, Lindel T. *Synthesis* 2003:1753. (b) Jacquot DEN, Lindel T. *Curr Org Chem* 2005;9:1551.
17. Einhorn C, Einhorn J, Marcadal-Abadi C. *Synth Commun* 2001;31:741.
18. An initial experiment conducted in chloroform indicated that a reaction occurred as the starting material was consumed, but no characterizable products were isolated.
19. A related adduct was obtained by Horne and co-workers on treatment of the 2-aminoimidazoles with NCS and methanol, in which the two newly installed methoxy groups were trans to one another. Olafson A, Yakushijin K, Horne DA. *J Org Chem* 1998;63:1248.
20. Baran and coworkers reported the oxidation of one of the 2-aminoimidazole moieties in ageliferin with peracetic acid leading to the formation of the dihydroxylated derivative. Subsequent treatment with NaHCO₃ led to the formation of the spiro fused imidazolone. See O' Malley DP, Li K, Maue M, Zografos A, Baran PS. *J Am Chem soc* 2007;129:4762. [PubMed: 17375928]

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Scheme 5.

Table 1

Conditions and yields for oxidative rearrangement of various THB derivatives

Entry	PG	X	Substrate	Conditions	Product	Yield/%
1	Me	H	1a	CHCl ₃ , rt, 4 h, 5	2a	82
2	Bn	H	1b	CHCl ₃ , rt, 4 h, 5	2b	80
3	MOM	H	1c	CH ₂ Cl ₂ , 40 °C, 26 h, 5	2c	50
4	SEM	H	1d	CHCl ₃ , rt, 16 h, 5	2d	60
5	DMAS	H	1e	^a	2e	NR
6	Bn	CO ₂ Me	1f	CHCl ₃ , 40 °C, 24 h, 6	2f	56

^aNo rearrangement was observed with either **5** or **6** at temperatures up to 60°C.

Table 2

Oxidation products of 2-azaimidazole derivatives

Entry	PG	X	Substrate	Conditions	Product (%)
1	Bn	N ₃	10	CHCl ₃ , 35 ° C, 24 h, 6	16 (70)
2	Bn	NPhth	14	CHCl ₃ , 35 ° C, 24 h, 6	17 (40)

Entry	PG	X	Substrate	Conditions	Product (%)
3	Bn	NH ₂	12	MeOH, rt, 4 h, 5

18 (59)

Entry	PG	X	Substrate	Conditions	Product (%)
4	DMA	N ₃	11	a	NR
5	DMA	NPhth	15	a	NR
6	DMA	NH ₂	13	MeOH, rt, 4 h, 6	19 (68)
7	DMA	NH ₂	13	H ₂ O, acetone, rt, 4 h, 5	20 (70)

^a No rearrangement was observed with either **5** or **6** at temperatures up to 60°C.