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Oxidative reactions of tetrahydrobenzimidazole derivatives with *N*-sulfonyloxaziridines

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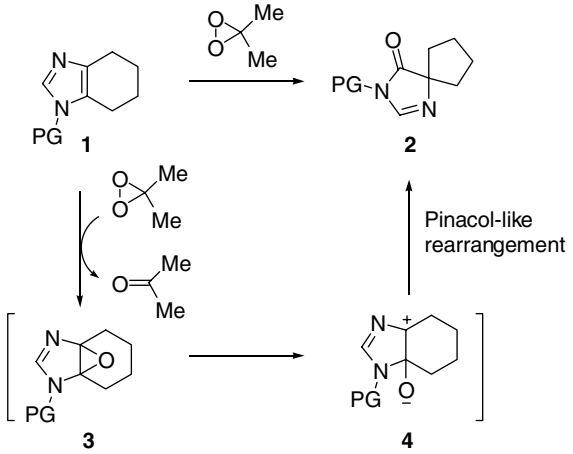
Abstract—An investigation of the utility of *N*-sulfonyloxaziridines to effect the oxidative rearrangement of tetrahydrobenzimidazoles to spiro fused 5-imidazolones is reported. In addition to the anticipated rearrangement manifold, it was found that 2-amino substituted derivatives afford products resulting 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).[2–5] 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]



Scheme 1.

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 equiv of phenyl sulfonyloxaziridine **5** in $CHCl_3$ led to a smooth rearrangement reaction,[11] providing the spiro fused 5-imidazolone **2a** in 82% yield (Table 1, entry 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

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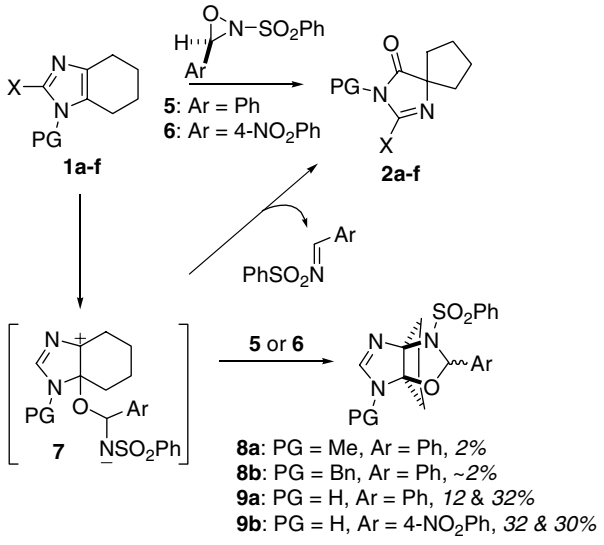
Table 1. Conditions and yields for oxidative rearrangement of various THB derivatives

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_2Cl_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_2Me	**1f**	$CHCl_3$, 40 °C, 24 h, **6**	**2f**	56

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

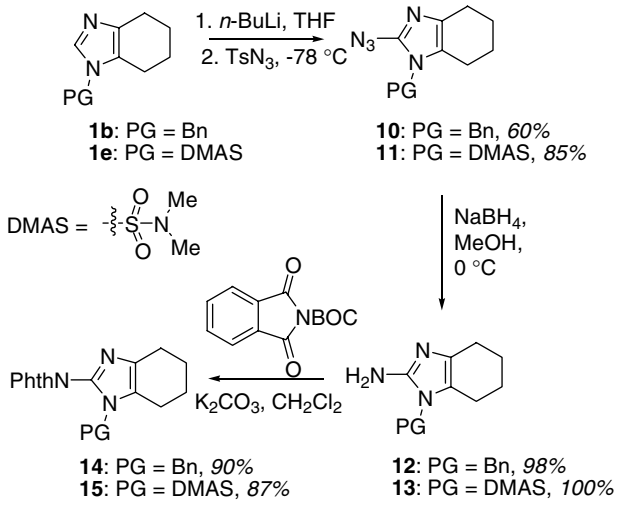
clue to the identity of this product was found in a study by Dmitrienko of the utility of *N*-sulfonyloxaziridines as oxygen transfer agents with indoles.[9,12] Instead of the desired oxindoles, formal [3+2] oxaziridine–alkene cycloadducts (across the indole 2,3-bond) were isolated as the major products (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 3a,7a-epoxide **3**, which opens to 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 imine and rearrangement to 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]



Scheme 2.

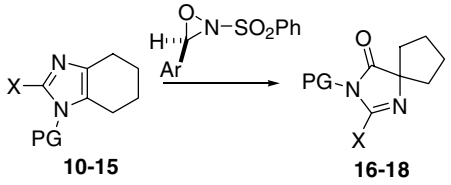
Given the success of this initial reaction we began to investigate the scope and limitations of this reaction. In the course of our earlier DMDO study,[2] we had assembled a collection of THB derivatives that differed in the nature of the N-substituent **1a**–**e** and the C2 substituent **1f**. These were investigated in the rearrangement chemistry with Davis' reagents (Ar = Ph, **5** or Ar = *p*-$NO_2C_6H_4$, **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 = Me_2NSO_2) derivative **1e**.[2] For the more electron deficient substrates, heating was required to effect rearrangement (Table 1, **1c**, entry 3), and in some cases the more reactive oxaziridine (Ar = 4-$NO_2C_6H_4$, **6**) was required (Table 1, **1e**, entry 6). We also investigated the reaction of unsubstituted tetrahydrobenzimidazole, that is, PG = H and found that it reacts with both Davis' reagents (**5**, Ar = Ph or **6**, Ar = 4-$NO_2C_6H_4$), 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 on-going 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 TsN_3. $NaBH_4$ reduction of **10** and treatment **12** with the modified Nefkens' reagent provided phthalimide derivative **14** (Scheme 3).[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 TsN_3 providing the 2-azido congener **11** (Scheme 3), which was easily reduced to amine **13**, which in turn was protected with a phthaloyl moiety on treatment with Nefkens' reagent, providing **15**.



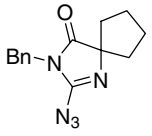
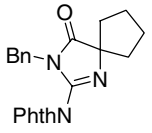
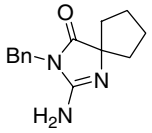
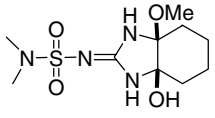
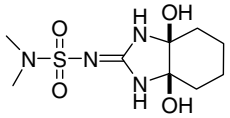
Scheme 3.

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** (Scheme 4), respectively (Table 2, entries 1 and 2). Unfortunately, this was not the case with the DMAS derivatives as neither the protected substrate **15** nor the azide **11** rearranged (Table 2, entries 4 and 5), however, we discovered that when the 2-amino derivative **13** was reacted with 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 the imidazolone carbonyl in the ^{13}C NMR spectrum at around $\delta_C = 180$ ppm was



Scheme 4.

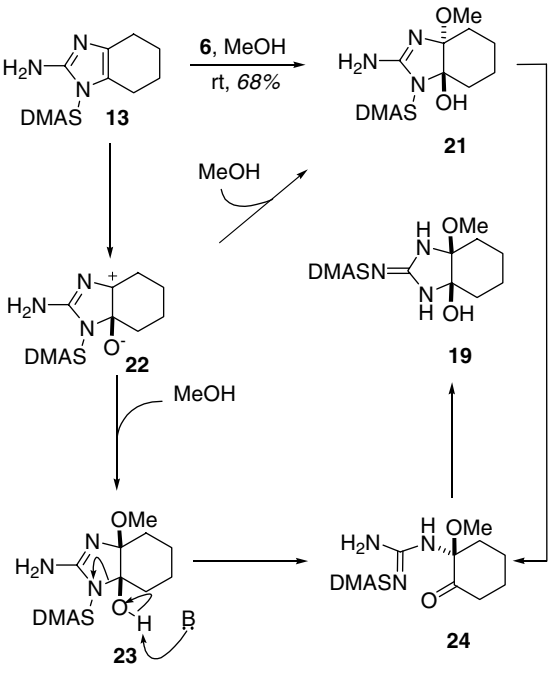
Table 2. Oxidation products of 2-azaimidazole derivatives

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)
3	Bn	NH_2	**12**	MeOH, rt, 4 h, **5**	 **18** (59)
4	DMAS	N_3	**11**	[a]	NR
5	DMAS	NPhth	**15**	[a]	NR
6	DMAS	NH_2	**13**	MeOH, rt, 4 h, **6**	 **19** (68)
7	DMAS	NH_2	**13**	H_2O, acetone, rt, 4 h, **5**	 **20** (70)

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

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 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 the formation of a dihydroxylation product (Table 2, **20**, entry 7). The constitution was assigned on the basis of the ^{13}C 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** (Table 2, entry 3).

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.



Scheme 5.

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' reagents to effect oxidation reactions of imidazole-containing substrates and its use in total synthesis efforts.

Acknowledgments

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