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The Effect of the Acidifying Group on the Regioselectivity of the Base-Induced Ring Opening of Hetero-Oxabicyclic [3.2.1] and [3.3.1] Systems

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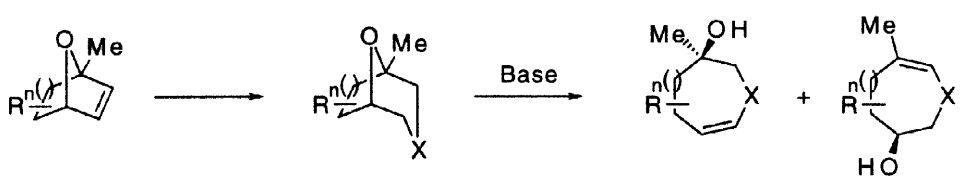
Abstract: Unsymmetrical 8-oxa-3-thiabicyclo[3.2.1]octane and 9-oxa-3-thiabicyclo[3.3.1]nonane underwent highly regioselective base-induced elimination but low selectivity was observed for the sulfonyl and the aza-oxa systems. A correlation between the regioselectivity of the reaction and the proton undergoing abstraction (i.e. equatorial *vs.* the axial proton) was made. © 1998 Elsevier Science Ltd. All rights reserved.

The synthesis of monocyclic medium-sized heterocycles is of interest owing to the difficulties associated with their construction and their potential utility as therapeutic agents. Methods which work well for five- and six-membered rings are unsatisfactory when applied to larger rings.[1,2] We have recently reported a base-induced C-O bond disconnection of meso [3.2.1] and [3.3.1] aza- and thiaoxabicyclic systems as an approach to enantiomerically enriched seven- and eight-membered nitrogen and sulfur heterocycles which are useful synthetic intermediates.[3] This communication describes our preliminary results on the regioselective base-induced ring opening of unsymmetrical hetero-oxabicyclic [3.2.1] and [3.3.1] systems (Scheme 1). The results revealed the influence of the acidifying group on the regioselectivity of the process. As discussed below, we attribute these results to the removal of the equatorial *vs.* axial proton which determines the level of regioselectivity in the base-induced ring opening.

Scheme 1



X = S, SO_2, NBOC
n = 1, 2

We have developed a versatile route to the 3-aza and 3-thia-8-oxa[3.2.1]bicyclic ring systems in 6 steps from furan (Scheme 2). The sequence has been carried out on a multigram scale from the oxa[2.2.1]bicycle **3** to the final [3.2.1]bicycles without purification of the diol and ditosylate intermediates. Reduction of the diester arising from cycloaddition of 2-methylfuran **2** and maleic anhydride **1** followed by protection of the resulting diol provided intermediate **3** in 75% yield for the three step sequence. Three straightforward steps were necessary for the incorporation of the heteroatom moiety: ozonolysis[4] and *in situ* reduction with $NaBH_4$, ditosylation followed by a double displacement of the bis *p*-toluenesulfonate with Na_2S or benzylamine.[5] Further oxidation of the thioether **4a** to the sulfone **4b** was carried out using *m*-CPBA. In order to perform α-lithiation in the aza series, the benzyl group in **4c** was replaced by the N-BOC group giving the substrate **4d**.[6]

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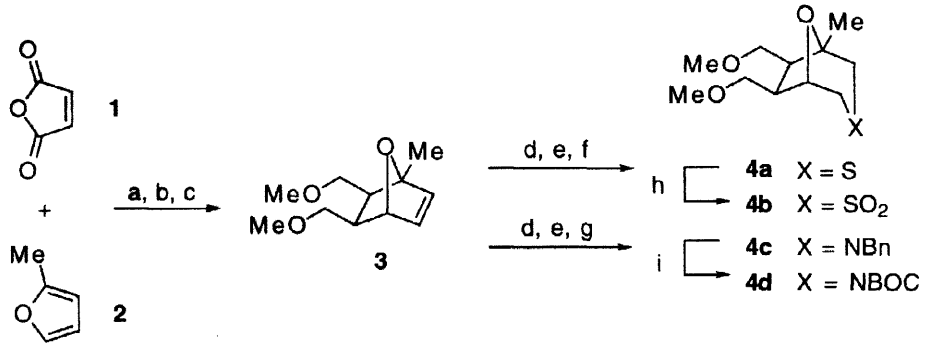
Scheme 2

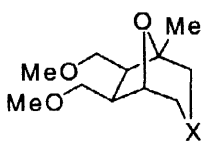
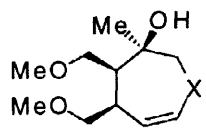
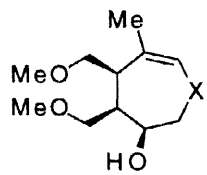


a) neat, rt. b) $LiAlH_4$, THF, rt. c) NaH, KH, MeI, 75% (3 steps). d) O_3, EtOH, 0 °C; $NaBH_4$. e) TsCl, pyridine, rt. f) Na_2S-$9H_2O$, DMF, reflux, 43% (3 steps). g) H_2NBn, $NaHCO_3$, DMF, reflux, 39% (3 steps). h) *m*-CPBA, CH_2Cl_2, rt, 89%. i) Pd/C, HCO_2NH_4, $(BOC)_2O$, EtOH, 51%.

The regioselective base-induced ring opening of **4a** was examined first. In our studies of the enantioselective ring opening of meso oxathiabicycles, we showed that benzene gave the best results and that an excess of base, 6 equivalents, was required for the reaction to go to completion.[3] Treating **4a** with an excess of LDA in benzene at ~5 °C gave a 95:5 mixture of thiepines **5a** and **5b** (Table 1, entry 1). The deprotonation occurred selectively at the "more accessible" methylene group, opposite to the bridgehead substituent giving a thiepine bearing a tertiary alcohol as the major product.[7] The use of a more sterically demanding amide base like LTMP (lithium tetramethylpiperidide) enhanced the regioselectivity of the reaction to 98:2 (Table 1, entry 2).

In contrast, the deprotonation of the analogous sulfone **4b** using 2 equiv. of LDA in THF at -78 °C gave low selectivity in favor of **5c** *vs.* **5d** (Table 1, entry 3). Reaction in toluene (Table 1, entry 4) or using the more sterically demanding LTMP (Table 1, entries 5 and 6) did not significantly improve the regioselectivity of the deprotonation. The nitrogen substrate **4d** was also readily ring-opened at -78 °C using 1.5 equiv. of *s*-BuLi in Et_2O,[8] leading to an equimolar mixture of regioisomers (Table 1, entry 7). All the eliminations in this study were assumed to be under kinetic control although this point has not been rigorously proven.

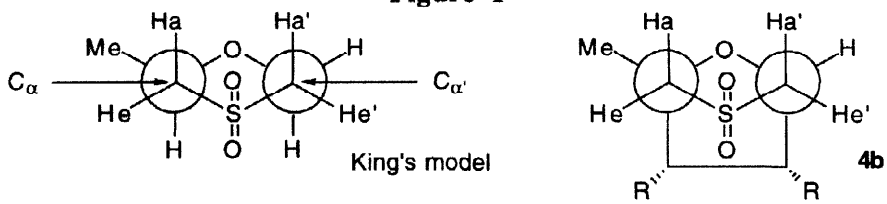
Table 1 Regioselective Base-Induced Ring Opening.

Entry	Substrate	Base	Conditions	Products	Ratio **a** : **b** [a]	Yield [b], %
						
1	**4a** X = S	LDA	PhH, 5 °C, 1 h	**5a / 5b**	95 : 5	93
2	**4a** X = S	LTMP	PhH, 5 °C, 1 h	**5a / 5b**	98 : 2	89
3	**4b** X = SO_2	LDA	THF, -78 °C, 1 h	**5c / 5d**	59 : 41	85
4	**4b** X = SO_2	LDA	$PhCH_3$, -78 °C, 1 h	**5c / 5d**	68 : 32	71
5	**4b** X = SO_2	LTMP	THF, -78 °C, 1 h	**5c / 5d**	54 : 46	75
6	**4b** X = SO_2	LTMP	$PhCH_3$, -78 °C, 1 h	**5c / 5d**	60 : 40	69
7	**4d** X = NBOC	*s*-BuLi	Et_2O, -78 °C, 1 h	**5e / 5f**	48 : 52	68 [c]

[a] The ratios have been determined by ^1H NMR. [b] Isolated yield of analytically pure products.
[c] Inseparable mixture.

The lack of selectivity in the deprotonation of the sulfone and N-Boc derivatives can be rationalized by considering the effect of the acidifying group on the proton which is abstracted. King and Rathore examined the rate of exchange of the α-hydrogens in a six-membered cyclic 1,4-sulfonylether.[9] This study concluded that α-equatorial hydrogens exchange faster than α-axial ones (using NaOD) because of the antiperiplanar orientation of the α-equatorial hydrogens with respect to the S-$C_{\alpha'}$ bond (which is aligned with the internal bisector of the O-S-O moiety) and more importantly, because of the antiperiplanar orientation of the α-equatorial hydrogen with respect to the C-O bond (Figure 1). The presence of a methyl group, situated in a position β to the sulfone, has neither a significant steric nor electronic effect on the exchange rate of He *vs.* He'. An identical geometry is found in substrate **4b** and its deprotonation followed the same pattern of reactivity as King's model and displayed low regioselectivity (Figure 1).

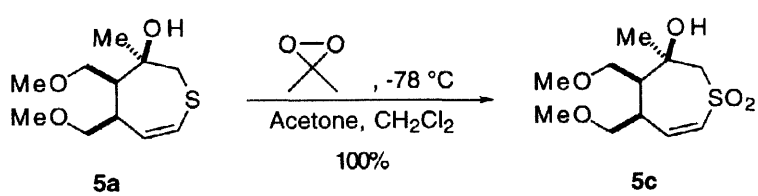
Figure 1



It is also well established that removal of the equatorial proton is favored in BOC-piperidines.[10] The low selectivity and the enhanced kinetic acidity could also be rationalized using King's arguments on the antiperiplanar orientation of the α-equatorial hydrogen with respect to the bridging oxygen.[9] The lack of selectivity in the sulfone and the N-BOC substrate strongly suggests a different mechanism for the deprotonation of the sulfide substrate.

The mechanism of deprotonation of the bicyclic sulfide **4a** is believed to be similar to the conversion of cyclohexene oxide to cyclohexenol using lithium amide bases which involves removal of a proton syn to the leaving group followed by the transfer of the lithium atom to the newly forming alkoxy group.[11] In our bicyclic substrates, this process corresponds to the removal of a pseudoaxial hydrogen assuming a chair conformation. An aggregate containing the substrate and the base is supported by the requirement of a non-polar solvent and an excess of the base. The large excess of base and the importance of the remote hydroxy protecting groups which was demonstrated in our previous study suggest that chelation of the remote ethers in association with the bridging oxygen seems to be essential; the Li ions may act as a Lewis acid in the activation of the substrate in the deprotonation-elimination sequence.[3]

From a synthetic perspective, although the sulfone **4b** failed to undergo selective deprotonation, chemoselective oxidation of the vinylsulfide **5a** using dimethyl dioxirane did provide the vinylsulfone **5c** as a single isomer (equation 1).

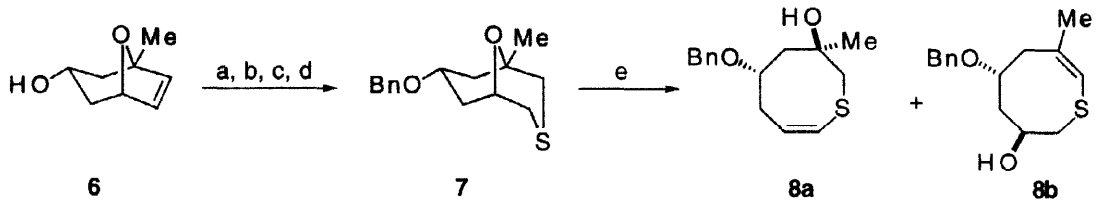


5a **5c** (1)

We also investigated the regioselectivity of the 9-oxa-3-thia-bicyclo[3.3.1]nonane system **7** which was prepared from the known oxabicyclic **6** (Scheme 3).[12,13] The hydroxy group was protected as its benzyl ether

and the incorporation of the sulfur atom was performed as previously described for **4a**. Treatment of **7** with 6 equiv. of LDA at rt for 2 days gave thiocines **8a** and **8b** in a 94:6 ratio as determined by ^{1}H NMR, although in a modest yield of 42%.

Scheme 3



6 **7** **8a** **8b**

a) NaH, KH, BnBr, THF, 80%. b) O_3, EtOH, 0 °C; $NaBH_4$. c) TsCl, pyridine, rt. d) $Na_2S{\bullet}9H_2O$, DMF, reflux, 40% (3 steps). e) LDA (6 equiv.), benzene, rt, 48 h, 42% (94:6)

In summary, the sequence reported herein constitutes a simple and valuable tool for the preparation of functionalized azepines, thiepines and thiocines. The correlation between the acidifying group and the regioselectivity implies that selective removal of the axial proton is necessary to achieve a synthetically useful reaction.

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