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Controlling thiiranium intermediates—a new route to an iNOS inhibitor

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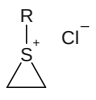
ABSTRACT

Our synthetic efforts towards an iNOS (inducible isoform of the nitric oxide synthase) inhibitor led us to the relatively unexplored field of generating and controlling the reactivity of chiral, unsymmetrical thiiranium species. We found that product regiochemistry depends on a tunable equilibrium, the understanding of which proved pivotal in defining a new route to a drug substance. The development of a new amidination method is also discussed.

Thiiranium or episulfonium salts **1** are useful synthetic intermediates that can be manipulated to give a variety of products. As sulfur analogues of epoxides, the chemistry of thiiranium species is dominated by the nucleophilic ring-opening of the three-membered ring. The ring-opening process of unsymmetrically substituted thiiranium rings is usually complicated by regioselectivity issues.[1]



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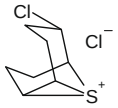

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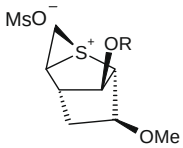

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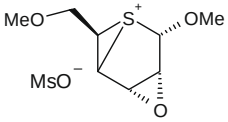

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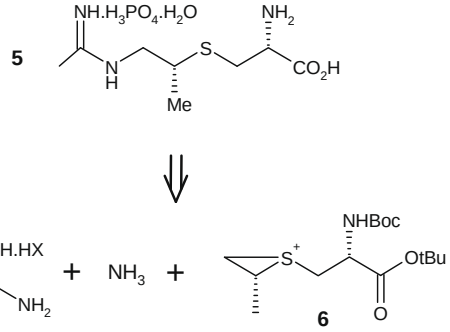
With a few exceptions such as **2**, the literature examples regarding the ring-opening of unsymmetrically substituted thiiranium intermediates are largely limited to thiofuranose and thiopyranose derivatives **3** and **4**. In these systems the regioselectivity is biased by virtue of the bicyclic ring constraints resulting in highly selective reactions.[2–4] In connection with our work on alternative syntheses for the iNOS (inducible isoform of nitric oxide synthase) inhibitor candidate **5**[5] we encountered issues with the regioselective ring-opening of the chiral thiiranium intermediate **6**. Unlike **3** and **4**, the reactivity of **6** is not governed by ring constraints and our understanding of this system became pivotal for the success of an alternative synthetic route.



Our synthesis began with premixing HMDS and commercially available (*S*)-2-bromopropionic acid **7** to afford the corresponding TMS ester, quantitatively, as a solution in THF. This was then added directly to a cold TBME (*tert*-butyl methyl ether) solution of the potassium thiolate of the cysteine derivative **8**. Thus, acid **9** was isolated in 90% yield after aqueous work-up and crystallisation. Under these conditions no evidence was found for formation of the undesired diastereoisomer. Carboxylic acid **9** was subsequently reduced to the primary alcohol **10** using borane generated in situ by the action of $NaBH_4$ on $BF_3{\cdot}Et_2O$.[6] In this fast and chemoselective reaction, alcohol **10** was obtained in high purity in 90% yield after methanolysis of the intermediate borates (Scheme 1). Again, no diastereoisomeric erosion was observed under these conditions. Alcohol **10** is a low melting-point solid but solutions of **10** obtained after work-up can be used directly in the next step.

During our attempts to activate alcohol **10** with mesyl chloride and triethylamine, we observed an interesting distribution of

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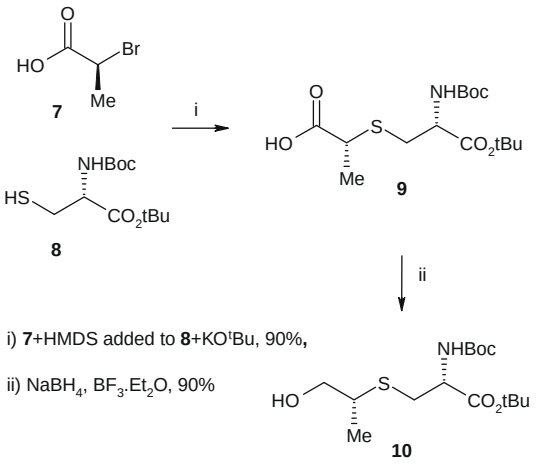
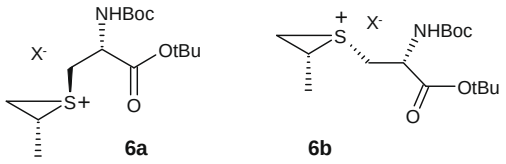


Scheme 1.

products which varied with time. The kinetic product under these conditions was the primary mesylate **11** which converts to the secondary topological isomer **12**; the latter being the major product after 1.5 h. At this point, primary chloride **13** starts to emerge and slowly becomes the major component of the mixture after five hours. Attempts to quench the reaction at this point and isolate **13** met with partial success. Batches of **13** isolated after five hours were sufficiently pure to be reacted in the next step but storage or attempted chromatographic purification resulted in exclusive formation of the isomeric chloride **14**. The same outcome was observed when the reaction was allowed to run for extended periods of time (Fig. 1).[7]

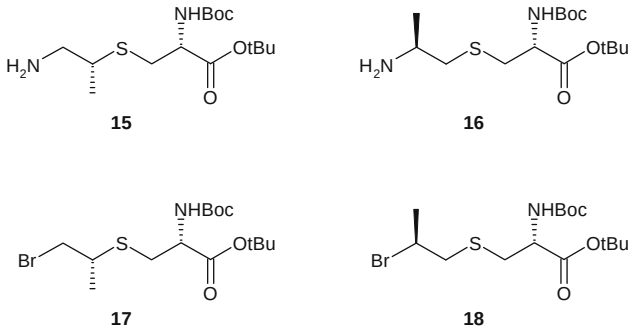
We propose that the sequential transformation of **10** into **14** is mediated by thiiranium species **6a** presumably generated by the intramolecular displacement of the leaving group by the sulfur atom, this being a reversible event. Episulfonium diastereoisomer **6b** is unlikely to be involved due to the increased steric demands of the *syn*-substituted thiiranium ring. Chloride **14** appears to be the thermodynamic sink of these series of equilibria where both the mesylate and chloride anions compete for both carbons of the electrophilic thiiranium ring. Compound **14** can be isolated in high purity and no regression to chloride **13** was observed in stored samples. We postulate that the intermediacy of **12** suggests that **6a** initially forms as a tight ion pair that allows reversible reaction of the poorly nucleophilic mesylate anion at the secondary carbon atom of the ring. Eventual separation of the ion pair by the solvent leads to individually solvated thiiranium cations and their subsequent capture by the more nucleophilic chloride anion thus generating **13** and **14**. Unlike intermediates **11**–**14**, the episulfonium species **6a** is not observed by NMR spectroscopy suggesting a short half-life.



Having established that activation of alcohol **10** results in mixtures of primary and secondary electrophiles, we realised that several criteria should be satisfied in order to achieve exclusive reaction through the primary species. Firstly, reaction of external nucleophiles with the primary species should be a fast and irreversible process. Secondly, the formation of the secondary electrophile should be reversible in order to constantly replenish the primary species consumed rapidly by the external nucleophiles. Finally, the concentration of thiiranium species **6a** should be as low as possible in order to limit potential reaction at the secondary carbon atom of the highly reactive ring system.

Initially we decided to investigate whether the chloride system **13**/**14** satisfies these requirements and could be exploited to furnish the key intermediate in the synthesis of **5**, namely homochiral amine **15**.[8] After a systematic screen of amination conditions, 7 M NH_3 in MeOH emerged as the most successful reagent system among a number of alternatives.[9]

Interestingly, when mixtures of chlorides **13** and **14** were quenched in 7 M NH_3 in MeOH, the desired amine **15** was obtained together with increased amounts of secondary chloride **14**. In fact, the degenerate chloride transformation leading to **14** is the dominant fate of **13** at higher temperatures and the reactions stall.



Neither **15** nor **16** was formed when pure chloride **14** was used in the amination reaction suggesting that secondary chloride **14** is inert to displacement by ammonia and does not equilibrate to **13**. In contrast, when mixtures of mesylates **11** and **12** of different relative proportions were quenched in 7 M NH_3 in MeOH, complete consumption of the electrophiles was observed. The yield and quality of amine **15** obtained from the mesylate system were significantly inferior to those obtained from the chloride analogue mainly due to by-product formation.[10] Despite the mesylate system satisfying the outlined criteria, it became clear that a less reactive system with a more stable primary species could be the key to the clean production of **15**.

We reasoned that the corresponding bromide system would offer the desired balance between stability and reactivity. Inclusion of LiBr in the standard mesylation reaction of alcohol **10** furnished (after quenching with aqueous NaBr solution), almost exclusively, the thermodynamic secondary bromide **18** as a single diastereoisomer with less than 5% of the primary isomer **17** being observed. When

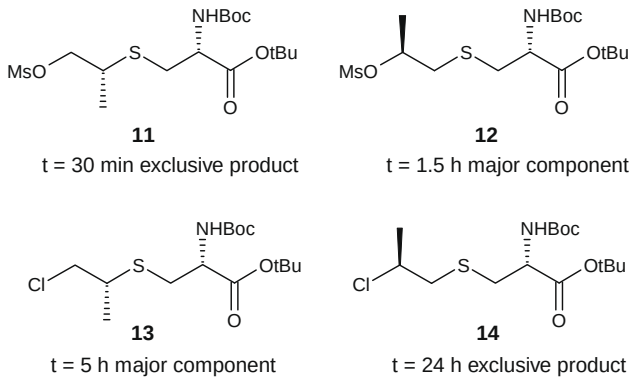
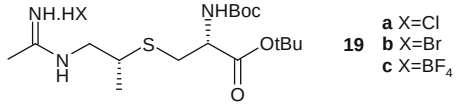
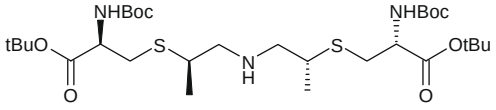


Figure 1. Change in product distribution during mesylation of alcohol **10**.

this 95:5 mixture of **18**–**17** was treated with 7 M NH_3 in MeOH, complete reaction was observed within a few hours and the desired primary alkyl amine **15** was isolated in 70% yield. This clearly demonstrates that both requirements for rapid equilibration between **17** and **18** and fast S_N2 reaction of **17** with ammonia operate in this system. The stereochemical integrity of the stereogenic centre adjacent to the sulfur atom was preserved through an overall double inversion process. The undesired isomer **16** was formed in consistently small amounts regardless of the leaving group associated with the secondary activated species **12, 14** and **18** which suggests that some regiochemical leakage was probably occurring through **6a**.

Having established that the bromide species are suitable for the amination reaction we then focused on installing the acetamidine group. In principle, the amidine functionality present in **5** can be installed directly by the displacement of bromide in the equilibrating mixture **17/18** by acetamidine. This approach did not work unless strong bases (methoxide) were included in order to generate the amidine free base. Such conditions were not tolerated well by our substrates and degradation became more dominant than amidination.[11] Having established that direct amidination was problematic, we decided to examine a stepwise approach. We initially found that amine **15** could be converted into **19a** when treated with acetamidine hydrochloride in a methanolic solution of ammonia. The minor amine isomer **16** does not appear to amidinate under these conditions hence this transformation also served as a purification step. We then demonstrated that it was possible to achieve a tandem amination/amidination of **17** in a single-pot process. The one-pot process required some tuning because the chloride anions present in the acetamidine salt (used in large excess) gave rise to significant amounts of **14**. The use of acetamidine hydrobromide[12] solved this problem but **19b** could not be obtained in crystalline form after aqueous work-up. We decided to perform salt exchange as part of the work-up and succeeded in isolating **19c** as a white crystalline solid. To the best of our knowledge, acetamidinium salts have not been reported as amidination reagents to date. An advantage of the in situ amidination was the suppression of **20** which probably arises from the reaction of **15** with **17**. In the non-telescoped amination reaction, impurity **20** forms in approximately 1–5%, but in the presence of acetamidinium salts (telescoped process) the primary amine **15** amidinates rapidly and therefore polyalkylation is avoided.





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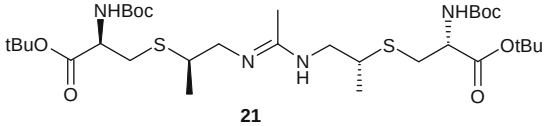

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During our attempts to optimise the new amidination reaction independently using authentic samples of **15** and acetamidine hydrochloride, we found that this process was actually a rapidly established equilibrium involving **15**, **19** and **21**. At low levels of the acetamidinium salt reagent, the higher amidine **21** was formed at significant levels. An authentic sample of **21** was prepared and was shown to revert back to **19** and **15** when treated with 7 M methanolic ammonia. As a result of this equilibrium, the yield of **19** was limited to 50% but work is in progress to understand this equilibrium and implement it more effectively in the one-pot process.

In summary, our route starts with the reduction of acid **9** to alcohol **10**, whose solution is taken forward into the activation step resulting initially in equilibrating mesylates **11** and **12** and eventually into the equilibrating mixture of bromides **17** and **18**, all presumably via thiiranium intermediate **6a**. After aqueous work-up,[13] the bromide species is treated with a solution of acetamidine hydrobromide in 7 M ammonia in methanol followed by work-up with aqueous ammonium tetrafluoroborate to furnish **19c** in 40% yield as a crystalline solid. This process spans six forward steps (in theory operating at an average yield of 85% each) and three sets of balanced equilibria, to deliver **19c** of comparable quality to **19a** obtained by our current supply route.[8] Finally, global deprotection of **19c** with phosphoric acid under carefully designed conditions, allows isolation of our iNOS inhibitor candidate as the monophosphate monohydrate salt **5** in 65% yield.[14]

To conclude, we have successfully synthesised iNOS inhibitor **5** via a short, cost effective route which pivots on an unprecedented counteranion-controlled double equilibrium mediated by an unsymmetrical thiiranium species.[15] We have also shown that acetamidine salts react readily with amines to form substituted acetamidines. We are currently looking to expand on the amidination reaction using these alternative reagents due to their inherent stability, safety and low cost.

References and notes

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6. Use of commercial borane in THF offered a good reaction and easier work-up but the product was contaminated with varying amounts of *n*-butanol (resulting from the reductive ring-opening of THF), depending on the date of manufacture and storage conditions of the reagent.
7. Alternative chlorinating agents such as PPh_3/NCS, $SOCl_2$ and PPh_3Cl_2 gave similar results with respect to the distribution of the chloride species and showed the same insensitivity towards base, temperature and solvent.
8. For the current supply route, see (a) Rassias, G.; Hermitage, S. A.; Sanganee, M. J.; Kincey, P. M.; Smith, N. M.; Andrews, I. P.; Borrett, G. T.; Slater, G. R. *Org. Proc. Res. Dev.* **2009**, *13*, 774–780; (b) Hermitage, S. A.; Panchal, T.; A.; Rassias, G.; Sanganee, M. J. PCT Int. Appl. 2005, WO 2005005377; *Chem. Abstr.* **2005**, *142*, 114456.
9. Use of azide chemistry was deliberately avoided due to scale-up and safety concerns and because of the poor performance of these thioether derivatives in the hydrogenation reactions we attempted previously (see Ref. 8). HMDS, hexamethylene triamine and ammonium salts in conjunction with bases failed to act as ammonia equivalents in this reaction. 7 M Ammonia in methanol outperformed the more dilute 2 M alternative and solutions of ammonia in water, ethanol, isopropanol and dioxane.
10. Attempts to prepare the mesylate species under chloride-free conditions using methanesulfonic anhydride also failed to improve the impurity profile. In the absence of other nucleophilic species the base required for this reaction invariably engaged the mesylate(s) and quaternary ammonium salts started to predominate for all bases used (Et_3N, DIPEA, Py). Quaternary salt formation was greatly limited by the use of 2,6-lutidine, but disappointingly, the parent bases could not be displaced from their quaternary derivatives by ammonia.
11. For the use of bis-Cbz protected acetamidine as nucleophile, see: Eustache, J.; Grob, A. *Tetrahedron Lett.* **1995**, *36*, 2045; Eustache, J.; Grob, A.; Lam, C.; Sellier, O.; Schulz, G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2961. This reagent would generate the Cbz-protected amidine. Hydrogenolysis of the Cbz-protected **15** was one of the weaknesses identified in our first route due to the poisoning effect of the sulfur

atom and the tendency of the aninothioether product to complex with palladium. The bis-Boc protected acetamidine was unstable in our hands.
12. Prepared by anion exchange from acetamidine hydrochloride and ammonium bromide in ethanol. When the hydrochloride salt was used, partial conversion of the bromide intermediate into a mixture of chlorides was observed.
13. It is imperative that the bromide **18** is put through an aqueous work-up prior to the amination/amidination reaction. This is to remove the excess mesyl chloride, otherwise significant levels of the corresponding sulfonamide of **15** are formed. The use of NaBr instead of brine in the work-up also ensures that the bromide system **17**/**18** is free of the problematic **13**/**14** analogue.
14. Equivalent in all aspects to the material used previously in clinical trials. The boron and fluoride content was <10 ppm.
15. For a similar system, see: Seki, M.; Shimizu, T. *Biosci. Biotechnol. Biochem.* **2001**, *65*, 973; Seki, M.; Yamanaka, T.; Kondo, K. *J. Org. Chem.* **2000**, *65*, 517. The influence of the leaving group is not discussed in these articles.