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An Unusual Samarium Diiodide Mediated Reductive Ring Contraction of a Tricyclic Oxazine to a Highly-Functionalized Cyclopentane and Cyclobutane

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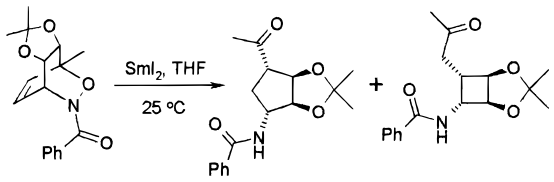
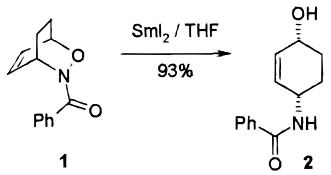
ABSTRACT



Samarium diiodide mediated reductive ring contraction of a substituted tricyclo[2.2.2]oxazine at 25 °C leads to a mixture of cyclopentane and cyclobutane rearrangement products with complete diastereoselectivity in each case. At −78 °C, the anticipated amidocyclohexanol reduction product is obtained exclusively, while the cyclopentane is the sole product at reflux in THF.

Samarium diiodide is a versatile single-electron reducing reagent which has been used widely in the past two decades for a variety of reductions,[1] pinacol coupling reactions,[2] Barbier-type reactions,[3] and many other rearrangements involving radical intermediates. The utility of samarium diiodide for the selective reduction of N−O bonds in oxazines was demonstrated by Keck and co-workers [4] for the preparation of amido alcohol **2** from the corresponding bicyclic oxazine **1** (Scheme 1).

Scheme 1. Samarium Diiodide Reduction of a Bicyclic Oxazine



In the course of our synthetic studies with enzymatically produced arene *cis*-dihydrodiols,[5] we obtained *cis*-dihydrodiol **3** as a single enantiomer from toluene via enzymatic *cis*-dihydroxylation using a whole-cell culture of the mutant microorganism *Pseudomonas putida* UV4. This organism contains a dioxygenase enzyme, which catalyses the arene *cis*-dihydroxylation, but lacks the diol dehydrogenase enzyme, which catalyses the subsequent step in the normal metabolic pathway.[5] Protection of the *cis*-dihydrodiol as a 1,3-dioxalane and then Diels−Alder cycloaddition with nitrosocarbonyl dienophile **4**, generated in situ by periodate

(1) Soderquist, J. A. *Aldrichimica Acta* **1991**, *24*, 15−23. Molander, G. A.; *Chem. Rev.* **1992**, *92*, 29−68. Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307−338.

(2) Nomura, R.; Matsuno, T.; Endo, T. *J. Am. Chem. Soc.* **1996**, *118*, 11666−11667.

(3) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693−2698. Curran, D. P.; Gu, X.; Zhang, W.; Dowd, P. *Tetrahedron* **1997**, *53*, 9023−9042.

(4) Keck, G. E.; McHardy, S. F.; Wager, T. T. *Tetrahedron Lett.* **1995**, *36*, 7419−7422.

(5) Boyd, D. R.; Sheldrake, G. N. *Nat. Prod. Rep.* **1998**, *15*, 309−324.

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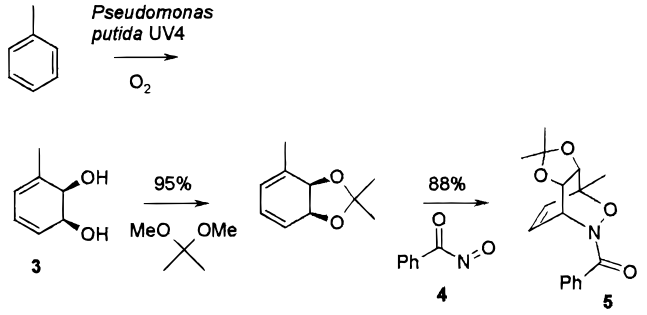
oxidation of benzohydroxamic acid, gave tricyclic oxazine **5** with complete regio- and diastereoselectivity (Scheme 2).

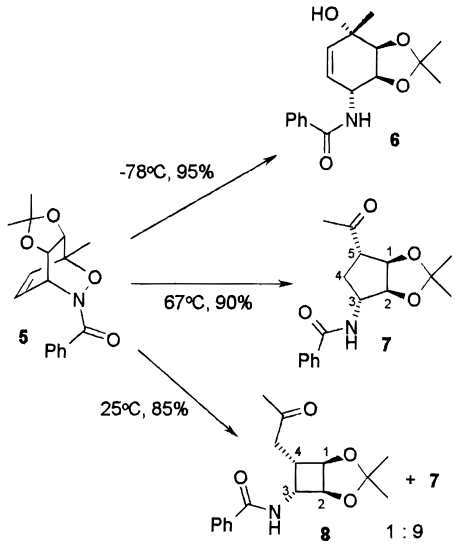
Scheme 2. Chemoenzymatic Preparation of Substituted Tricyclic Oxazine **5**



Samarium diiodide was chosen as the reagent for the mild and selective reduction of **5** to give amido alcohol **6**.

When the reductive cleavage was carried out at 25 °C, with an excess of samarium diiodide, two products (**7** and **8**, Scheme 3) were isolated (ratio 9:1 by ^{1}H NMR spectroscopy), with a combined yield of 85%. Neither of the products had spectroscopic data compatible with the expected amido alcohol product **6**. The products were separated using preparative thin-layer chromatography, and mass spectroscopic analysis indicated that they were isomeric. IR and NMR spectroscopy revealed that both products were methyl ketones and that both retained the dioxalane-protected *cis*-diol functionality.

Scheme 3. Samarium Diiodide Reduction of Oxazine **5** at Different Temperatures



Unequivocal confirmation of the cyclobutane structure for **8** was obtained by X-ray crystallographic analysis.[6] The absolute configuration of **8** was assigned from the relative stereochemistry determined in the crystal structure on the assumption that the configurations at carbons C-2 and C-3 had remained unchanged: it is difficult to imagine a mechanism that would result in the simultaneous inversion of configuration at both of these positions.

Careful examination of the crude product mixture by NMR spectroscopy revealed that **7** and **8** were formed as single diastereoisomers indicating that the two ring contractions had occurred with complete stereochemical control. The relative configuration of cyclopentane **7** was assigned by ^{1}H NMR spectroscopic analysis.[6] The key assignments are the *trans* relationship between the methine hydrogens H-1 and H-5 (J = 0 Hz, consistent with a 90° dihedral angle) and the *cis* relationship between H-1 and H-2 (J = 5.9 Hz). Again, assuming that the configurations at C-2 and C-3 remain unchanged during the ring contraction, this also establishes the absolute configurations at C-1 and C-5.

Attempts to optimize the formation of either or both of the rearrangement products by variation of the reaction conditions led to some interesting observations. While a large excess of commercial samarium diiodide solution at first appeared to be necessary to obtain complete conversion of the starting material, rigorous exclusion of air and moisture and preparation of a fresh SmI_2 solution [7] immediately prior to reaction established that 2 equiv of the reductant was required. Performance of the reaction at −78 °C led to exclusive formation of amido alcohol **6**, while reaction in refluxing THF (67 °C) led to formation only of cyclopentane product **7**. So far we have been unable to improve the ratio of products **8**:**7** to better than 1:4 (0.5 h at 0 °C, at which temperature small amounts of amido alcohol **6** were also observed).

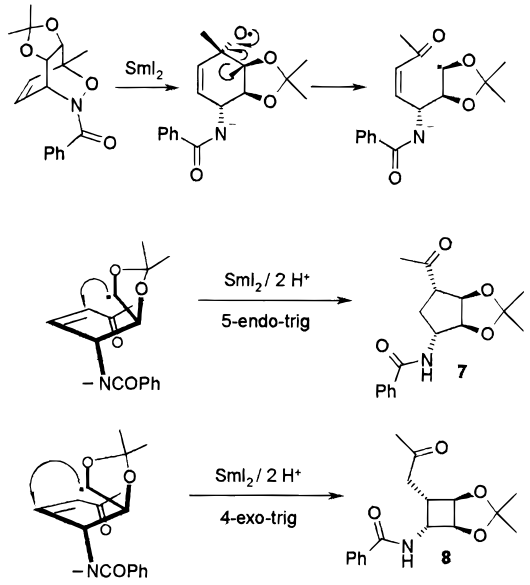
Investigation of the mechanism(s) of these unusual rearrangements is ongoing, but at this early stage a possible mechanistic pathway may be conjectured. To obtain the methyl ketone functionality it would seem likely that the initial transfer of an electron from the Sm^{2+} ion to the N−O bond results in an oxygen-centered radical and an anion on the amide nitrogen (Scheme 4).

Under "normal" N−O reduction conditions a second electron is transferred from another Sm^{2+} ion to give an oxyanion which is then protonated either immediately or during workup. This process is observed when the reaction is carried out at −78 °C. At higher temperatures it appears that the oxygen-centered radical fragments to give an oxygen-stabilized, carbon-centered dioxalanyl radical. All attempts to effect this rearrangement starting from amido alcohol **6**, under acidic or basic conditions, have failed to produce either of the ring-contraction products **7** or **8**. One possible explanation is that the radical is transferred from oxygen to C-1 in a concerted process involving formation of the C−O double bond and homolytic fission of the C-1/C-6 bond. Stereoselective addition of this radical to the top face of the alkene double bond, possibly with coordination assistance by Sm^{2+} or Sm^{3+}, would lead to the observed products via

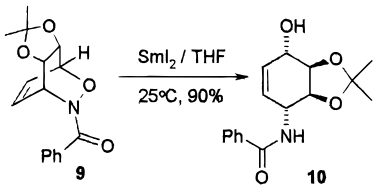
(6) See Supporting Information.

(7) Namy, J. L.; Girard, P.; Kagan, H. B.; Caro, P. E. *Nouv. J. Chim.* **1981**, *5*, 479−484.

Scheme 4. Suggested Mechanism for the Ring Contractions to the Cyclopentane **7** and Cyclobutane **8**



Scheme 5. Reduction of Desmethyl Oxazine **9** with Samarium Diiodide To Give Amido Alcohol **10** without Competing Ring Contractions



a 5-endo-trig or 4-exo-trig process. Ring closure to the five-membered ring would be favored from ring-strain considerations, but addition of the electron-rich nucleophilic radical to the alkene double bond would also be facilitated by the conjugation of this alkene to the ketone. This could account for the unusual ring closure to the cyclobutane. Reduction of the rearranged radical with a second Sm^{2+} ion and then protonation during workup would complete the process. While we currently have no direct evidence to support this mechanism, there have been a few reported examples of this type of rearrangement process involving dioxalanyl radicals. For example, Murphy and co-workers have demonstrated that dioxalanyl radicals generated from nitrite esters undergo stereoselective intramolecular additions to alkenes.[8]

One observation which is not fully explained by our mechanistic interpretation is that the des-methyl Diels−Alder adduct **9** gives *only* amido alcohol reduction product **10** under any of the reaction conditions described (Scheme 5) and cannot be persuaded to undergo rearrangement. It is possible that the presence of the extra methyl group in **5** sterically inhibits approach of further Sm^{2+} ions to the tertiary oxygen radical long enough for fragmentation to be preferred over a second electron-transfer process.

This unusual rearrangement process has provided a new method for the preparation of highly functionalized cyclopentane and cyclobutane ring systems with a high degree of stereochemical control. These enantiopure products have four asymmetric centers and are readily prepared in synthetically useful quantities from toluene in four steps. Utilizing the enantiocomplementary strategies for obtaining both enantiomers of the arene *cis*-dihydrodiols [9] developed in these laboratories, there is also ready access to both antipodes of the rearrangement products. Synthetic applications for these new and versatile additions to the chiral pool are currently under investigation.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **5**−**8** and X-ray crystallographic data for compound **8**. This information is available free of charge via the Internet at http://pubs.acs.org.

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(9) Allen, C. C. R.; Boyd, D. R.; Dalton, H.; Sharma, N. D.; Brannigan, I.; Kerley, N. A.; Sheldrake, G. N.; Taylor, S. C. *Chem. Commun.* **1995**, 117−118.