The First Stable Enantiomerically Pure Chiral N−H Oxaziridines: Synthesis and Reactivity

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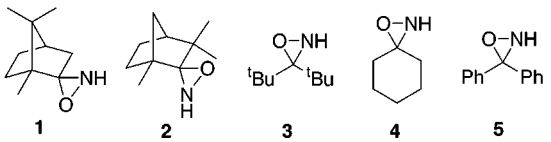
N−H oxaziridines, first reported in the early 1960s, induce amination of nitrogen, oxygen, sulfur and carbon nucleophiles,[1] including aziridination of alkenes and amination of enolates. To date, of the very few N−H oxaziridines that are known, no chiral nonracemic N−H oxaziridine has been isolated. We report here the preparation of the first stable enantiomerically pure chiral N−H oxaziridines **1** and **2** together with a brief survey of their derivatization and chemical reactivity. Also reported is the first example of an *N*-sulfenyloxaziridine, the first enantiomerically pure chiral *N*-alkoxycarbonyloxaziridine, and the first enantiomerically pure *N*-phosphinoyloxaziridine chirally functionalized at carbon.

Due to their instability, N−H oxaziridines must generally be prepared and used in dilute solution. The only one that has been isolated as a stable compound in pure form is compound **3**,[2] and the chemical reactivity of only one has been thoroughly investigated (compound **4**).[1] Their instability no doubt accounts for the dearth of knowledge and awareness of N−H oxaziridines. Nevertheless, this functional group appears to offer an intriguing alternative potential solution to the problem of asymmetric electrophilic nitrogen transfer, usually accomplished by use of chiral auxiliary chemistry.[3] For this reason we turned our attention to the synthesis and chemistry of chiral, nonracemic N−H oxaziridines **1** and **2**, derived from camphor and fenchone, respectively.



1 **2** **3** **4** **5**

N-Acyl- and *N*-alkoxycarbonyloxaziridines have been shown to transfer their nitrogen moiety to a number of sulfur, nitrogen, phosphorus, and carbon nucleophiles and tend to be more stable. There has, however, been only one report of a chiral enantiomerically pure *N*-acyloxaziridine.[4] Most [5] *N*-acyl- and *N*-alkoxycarbonyloxaziridines have been prepared by oxidation of N-protected imines of benzaldehydes.[6] *N*-Sulfonyl-[7] and *N*-phosphinoyloxaziridines,[8] useful oxygen transfer agents, are prepared in the same way. This method is efficient for the oxidation of *N*-sulfonylimines, which are commonly easily prepared and stable, but is less satisfactory for the oxidation of *N*-phosphinoylimines, which are more prone to hydrolysis. *N*-Acylimines are even less stable and are commonly only available when prepared from a ketone that is nonenolizable and contains α-electron-withdrawing groups.[9]

Derivatization at the nitrogen atom of an oxaziridine, as opposed to oxidation of the derivatized imine, could therefore provide a useful alternative method of preparation of N-functionalized oxaziridines, if the corresponding N−H oxaziridines can themselves be readily prepared. Indeed, some examples of acyl derivatives have been prepared *in situ* by use of solutions of unstable N−H oxaziridines.[4,10]

N−H oxaziridines have been prepared from ketones by treatment with hydroxylamine-*O*-sulfonic acid or precursors of chloramine.[1] Neither of these two techniques proved successful for camphor or fenchone, possibly due to the steric hindrance about the ketone moiety. We therefore sought an alternative and selected oxidation of the primary (N−H) imine with peracid, a method used in the preparation of N−H oxaziridines **3** and **5**, derived respectively from di-*tert*-butyl ketone and benzophenone.[6]

Preparation of primary imines by simple condensation of ammonia with ketones is problematic, as primary imines are commonly unstable above room temperature. Sealed tube methods have been used,[11] but they are unreliable. The primary imines **6** and **7**, derived from camphor and fenchone, respectively, are, however, both stable up to ca. 30 °C and were prepared via the nitrimines **8** and **9**.[12] Nitrosation/rearrangement of the corresponding oximes **10** and **11** followed by ammonolysis of the resulting nitrimines in THF[13] gave the primary imines in quantitative yields. Oxidation of each imine with 1 equiv of *m*-CPBA at −30 to −40 °C in dichloromethane took place to give the N−H oxaziridines **1** and

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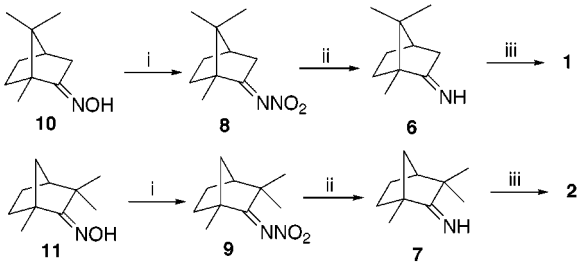
Scheme 1



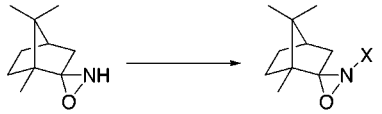
2, in 94% and 86% yields respectively, on a 20 g scale (Scheme 1).

These N−H oxaziridines are remarkably stable in their pure form in comparison to their simpler analogues and can be kept at 5 °C for at least 6 months without decomposition. They are stable to silica gel chromatography. The camphor-derived oxaziridine **1** is crystalline and can be heated under reflux in THF solution for at least 6 h without decomposition, although it is unstable under reflux in toluene. In this context, it is interesting to note that **1** has been implicated as a reactive intermediate in the thermal rearrangement of camphor oxime.[14] The fenchone-derived oxaziridine **2**, an oily liquid, is stable under reflux overnight in THF and toluene solutions.

N−H oxaziridines **1** and **2** were each shown by ^{1}H NMR spectroscopy to consist of a pair of diastereoisomers in a ratio of about 60:40. It is possible in principle to form both *endo* and *exo* isomers of the oxaziridine ring, depending upon the direction of attack of the oxidant. An unusual feature of nitrogen-containing three-membered heterocycles is that there is a rather high barrier to inversion at nitrogen.[15] It is therefore possible that oxidation of imines **6** and **7** could give rise to four different diastereoisomers each. We believe, on the basis of chemical derivatization coupled with NMR spectroscopic evidence, that the diastereoisomers observed in this case arise from the two configurations at the nitrogen atom, the result of *endo* delivery of the oxygen atom to the camphor system to give **1**, and *exo* delivery to the fenchone system to give **2**.

Although there have been no reports of the barrier to inversion of nitrogen atoms in N−H oxaziridines, studies on the related *N*-alkyl/aryl-,[1,16] *N*-acyl-,[1,17] *N*-alkoxycarbonyl-,[1] *N*-sulfonyl-,[18] and *N*-phosphinoyloxaziridines[19] show that the barrier to N-inversion appears to be lowered in oxaziridines where the nitrogen atom is conjugated with an electron-withdrawing subtituent, in comparison to *N*-alkyloxaziridines.[20] *N*-Alkyl and *N*-chlorooxaziridines[21] are, however, configurationally stable at room temperature. Apart from some small changes in line width and chemical shift, the N−H NMR signals of **1** (δ 4.97 and 4.83 at 25 °C) showed no significant change in their appearance over the temperature range −70 to +50 °C. The data suggest a Gibbs free energy of activation for nitrogen inversion of greater than 16 kcal mol^{-1}.

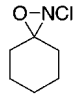
We reasoned that the identity of the isomers of **1** might be proven by efficient derivatization at the nitrogen atom (eq 1). Reactions of **1** with acetyl chloride, tosyl chloride,



(1)

for **12**, t-BuOCl, Et_2O, –78 °C — **12**, X = Cl; 85%
for **14**, $PhSO_2Cl$, DMAP, CH_2Cl_2, RT — **14**, X = SO_2Ph; 62%
for **15**, Ph_2POCl, DMAP, CH_2Cl_2, RT — **15**, X = $POPh_2$; 37%
for **19**,**20**, RO_2CCl, pyridine, CH_2Cl_2, 0 °C to RT — **19**, X = CO_2Me; 95%; **20**, X = CO_2Et; 89%
for **21**, C_6F_5SCl, py, CH_2Cl_2, RT — **21**, X = SC_6F_5; 41%

ethyl chloroformate, or diphenyl phosphinic chloride in the absence of base gave none of the desired derivatized oxaziridines. A new material, an oxidant capable of oxidizing thioanisole, was isolated in low yields from all of these reactions and was proven by single-crystal X-ray crystallography to be the *N*-chlorooxaziridine **12**, with the oxygen atom of the oxaziridine moiety endo as expected and the chlorine atom pointing away from the bridgehead methyl group. Compound **12** was also formed in 31% yield in a few seconds as a single diastereoisomer, together with camphor in 35% yield, by treating **1** with anhydrous hydrogen chloride in 1,4-dioxane at −40 °C. It is possible that one molecule of the N−H oxaziridine (or N-protonated oxaziridinium species) oxidizes the hydrogen chloride to an electrophilic chlorine species, which then chlorinates another molecule of the oxaziridine, so accounting for the approximately 1:1 mixture of camphor to *N*-chlorooxaziridine in the product. Compound **12** was indeed produced in 85% yield, again as a single diastereoisomer, by treatment of **1** with the electrophilic chlorine reagent *tert*-butyl hypochlorite in ether at −78 °C. The barrier to inversion at nitrogen in the related spirocyclohexane *N*-chlorooxaziridine **13** is known to be high from studies on the resolved material,[21] suggesting that the stereocontrol observed in the formation of **12** is kinetically controlled.



13

Chiral *N*-sulfonyloxaziridines are useful asymmetric oxidants, and a number have been prepared previously by Davis, ourselves, and others.[7] In each case, these oxaziridines were prepared by oxidation of the corresponding imines. We have been able to prepare the known *N*-phenylsulfonyloxaziridine **14** as a single diastereoisomer in 62% yield by treatment of **1** with benzene sulfonyl chloride in the presence of DMAP in dichloromethane.[22]

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(20) Typical values in kcal mol^{-1}: *N*-alkyl, 25−34; *N*-chloro, 32; *N*-sulfonyl, 20−21; *N*-alkoxycarbonyl, 18; *N*-acyl, 11−12; *N*-phosphinoyl, 13. See refs 1, 16−19, and 21.
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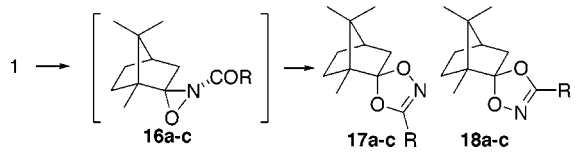
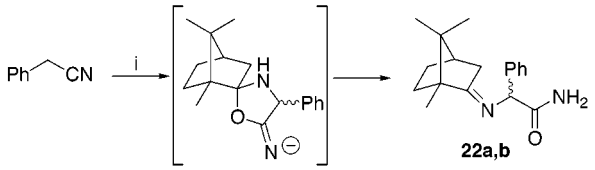
Scheme 2



a, R = p-NO_2Ph; b, R = Me; c, R = Ph
RCOCl, DMAP, CH_2Cl_2, RT, or $(RCO)_2O$, CH_2Cl_2, RT

Scheme 3[a]



(i) LHMDS, THF, –78 °C; **1**; 78%

N-Phosphinoyloxaziridines are also useful oxidants.[8] Although asymmetric reactions have been carried out using this type of oxaziridine in enantiomerically enriched form, the asymmetric center was in these cases the phosphorus atom, and not the carbon atom of the oxaziridine moiety. We have been able to prepare the first example of an enantiomerically pure *N*-phosphinoyloxaziridine chirally functionalized at the carbon atom. Reaction of **1** with diphenyl phosphinic chloride in the presence of DMAP gave **15** in 37% yield, again as a single diastereoisomer. *N*-Phosphinoyloxaziridines are known to be somewhat less reactive than their *N*-sulfonyl counterparts,[23] and indeed **15** is a poor oxidant: it reacts only very sluggishly with sulfides at room temperature.

It has been reported that *N*-acyloxaziridines are more stable than their analogous N−H oxaziridines.[1] As yet, however, we have not been able to achieve an effective acylation of N−H oxaziridine **1**. Attempted acylation of **1** with *p*-nitrobenzoyl chloride in the presence of DMAP, gave two new compounds, one with oxidizing properties (presumed to be *N*-acyloxaziridine),[24] and the second, in trace amount, not an oxidant. Workup followed by attempted chromatographic purification gave only the latter product, and in much larger yield (63%) than expected from TLC analysis of the reaction mixture. This product was shown by ^{1}H NMR spectroscopy to be a mixture of two diastereoisomeric products in about a 1:1 ratio, both also isomers of the expected *N*-acyl oxaziridine **16a**. The data are consistent with dihydrodioxazoles **17a** and **18a**, which could arise from *N*-acyloxaziridine by rearrangement (Scheme 2). Acylation of **1** using acetic anhydride proceeded more cleanly, only *N*-acyl oxaziridine **16b** being observed in the product mixture by ^{1}H NMR spectroscopy before attempted purification. Treatment of this material with silica gel at room-temperature overnight induced complete transformation into the dihydrodioxazoles **17b**/**18b**; the two diastereoisomers were isolated in ca. 90% yield overall, and again in a 1:1 ratio. Such rearrangements, for example, of cyclohexanone *N*-acetyloxaziridine[25] and *N*-acylaziridines,[26] have previously been observed, although they generally require heating of the reaction mixture. A related dihydrodioxazole has been shown to undergo reductive cleavage to give the parent ketone and benzamide.[27] Hydrogenolysis of **17c**/**18c**, obtained from the reaction of **1** with benzoyl chloride, over palladium at room temperature indeed gives camphor and benzamide as products. The fact that we observe formation of two isomers during the rearrangement leads to the interesting conclusion that the rearrangement is not concerted, but must take place through an intermediate in which the oxaziridine carbon atom has lost its stereogenicity.

Efficient functionalization of the nitrogen atom of **1** was finally achieved by reaction of the N−H oxaziridine with various derivatizing agents in the presence of base. Formation of *N*-methoxycarbonyl **19** and *N*-ethoxycarbonyl **20** derivatives was effected in 95% and 89% yields, respectively, by the reaction of **1** with methyl or ethyl chloroformate and pyridine in dichloromethane solution. Inspection of the ^{1}H NMR spectra of the products suggests that each of these reactions gave the product as a single diastereoisomer; taken in conjunction with the high yields, this demonstrates that **1** is indeed a mixture of two isomers differing in the configuration at the pyramidal nitrogen atom and not at the carbon atom of the three-membered ring, none of the stereoisomers at that carbon atom being observed in either case.

We have also prepared the first *N*-sulfenyloxaziridine **21**, a previously unreported class of oxaziridine derivative and also an oxidant,[24] again as a single diastereoisomer, in 41% yield, by treatment of **1** with pentafluorobenzene sulfenyl chloride and pyridine in dichloromethane at room temperature. The thiooxime was also isolated in 10% yield together with bis(pentafluorophenyl) disulfide (20%) and camphor (28%).

We have identified conditions under which nitrogen transfer takes place to enolates and related carbanions: for example, deprotonation of phenylacetonitrile and treatment with **1** provides a 78% yield of **22a**/**b** as a ca. 1.5:1 mixture of diastereoisomers at the new stereogenic center. During this reaction, the nitrogen atom has been transferred together with the camphor moiety, water has been eliminated to generate an imine unit, and the nitrile group has been hydrolyzed to a primary amide, we believe *via* a cyclic intermediate (Scheme 3).

In summary, preparation of the first stable enantiomerically pure chiral N−H oxaziridines is reported together with a brief survey of their derivatization and chemical reactivity. These N−H oxaziridines exist as mixtures of diastereoisomers at the pyramidal nitrogen atom. Also reported are the first example of an *N*-sulfenyloxaziridine, the second enantiomerically pure chiral *N*-acyloxaziridine, the first enantiomerically pure *N*-alkoxycarbonyloxaziridine, and the first enantiomerically pure *N*-phosphinoyloxaziridine chirally functionalized at carbon. NMR spectroscopy suggests that all N-substituted oxaziridines were isolated as single diastereoisomers with the N-substituent oriented in thermodynamically most favored position away from the bridgehead methyl group, or perhaps as rapidly inverting isomers, irrespective of the stereochemistry of the N−H oxaziridine starting material. Were the barrier to nitrogen inversion high in the products, this outcome would presumably result from much faster reaction of the less stable isomer of the NH oxaziridine; if, as seems likely,

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(24) Potassium iodide/sodium hydroxide test.
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the barrier to inversion is low in the products, this outcome would arise from inversion at nitrogen and formation of a thermodynamic mixture of isomers.

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Supporting Information Available: Full experimental details; A4 photocopies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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