Hydroxylation of Dihydroisoxazoles Using *N*-Sulfonyloxaziridines

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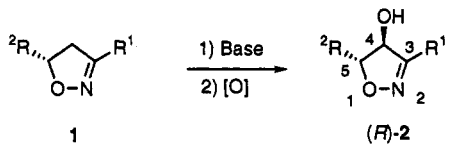
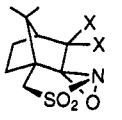
In connection with our interest in the oxidation of enolates using *N*-sulfonyloxaziridines[1] and the chemistry of 4,5-dihydroisoxazoles (DHIs; isoxazolines),[2] we describe results of a study of the hydroxylation of DHIs **1** via the aza-enolate anions to 4,5-dihydro-4-isoxazolols **2**, valuable intermediates in the synthesis of aminopolyols and amino sugars.[3] Jäger et al. first prepared **2** in moderate yield by reaction of the anions of **1** with borates and subsequent oxidative workup.[4] Somewhat better yields were achieved using oxygen as the oxidant.[5] Alternate, recently developed routes to the 4-isoxazolols **2**, employ nitrosative cyclization[2b] and tandem nitroaldol strategies.[6] None of these procedures affords enantiomerically enriched **2**.



1 (*R*)-**2**

a: R^1=Ph, R^2=H
b: R^1=PhS, R^2=H
c: R^1=$PhSO_2$, R^2=H
d: R^1=PhO, R^2=H
e: R^1=Ph, R^2=*n*-C_4H_9
f: R^1=Ph, R^2= spiro(C_4H_8)



(+)-**3**a: X=H
b: X=Cl
c: X=OMe

The enolate oxidation protocol, the hydroxylation of an enolate with an aprotic oxidizing reagent, is one of the most efficient methods for the introduction of a hydroxyl group adjacent to a carbonyl.[1,7,8] Vedejs' MoOPH reagent,[9] O_2,[10] and *N*-sulfonyloxaziridines[1,7] have all been utilized for this purpose. The use of (camphorylsulfonyl)oxaziridine derivatives **3** is advocated, whether or not a chiral product is desired, because of their efficiency, lack of side products, and commercial availability.[1,7]

Jäger et al. generated DHI aza-enolate anions by treatment with LDA at −78 °C.[3] The addition of HMPA was required because of the low reactivity of these anions, and the fact that they isomerize above −78 °C to the corresponding ring-opened *N*-hydroxy-2-propenimides. In our work the DHI anions were generated by addition to 1.2 molar equiv of LDA in THF at −78 °C. Enolate formation failed with NaHMDS or KHMDS presumably due to their lower basicity. Treatment of **1c** and **1d** with LDA led to decomposition and *N*-hydroxy-2-propenimidate formation, respectively (Table I, entries 10 and 11). Thus, there are some limitations on the synthesis of 4-isoxazolols imposed by anion stability.

Hydroxylation was accomplished by addition of a THF solution of an equivalent amount of the oxaziridine (+)-**3** to the anions of **1** at −78 °C, and the crude products were purified by preparative TLC. The 4-isoxazolols **2** gave satisfactory elemental analyses and a characteristic ^{1}H-NMR multiplet at δ 2.3–2.6 (OH) which is exchangeable with D_2O. The ee values were determined by NMR after conversion of **2** into the corresponding Mosher esters (Table I).

In contrast to earlier reports on the low reactivity of DHI anions in the absence of HMPA,[2-4] hydroxylation with (+)-[(8,8-dichlorocamphoryl)sulfonyl]oxaziridine (**3b**) (8,8-dichloro-1,7,7-trimethyl-2′-(phenylsulfonyl)spiro-[bicyclo[2.2.1]heptane-2,3′-oxaziridine]]) afforded **2a** in 50% yield and 50% ee (entry 3). Addition of HMPA improved the ee to 56% but decreased the yield to 40% because of difficulty separating the product from this additive (entry 4). We found, however, that the addition of tetramethylethylenediamine (TMEDA), which is more easily removed than HMPA, improved both the yield and stereoinduction (entry 5). The additive HMPA is thought to increase enolate reactivity by making it more accessible to the electrophile.[11] Although TMEDA has recently been shown to increase the reactivity of lactone enolates toward hydroxylation,[12] its mechanism of action is unclear.[13]

The hydroxylated stereocenter C-4 in **2** is predicted to have the *R* configuration on the basis of the chiral recognition mechanism developed for the hydroxylation of enolates by **3**.[1,14] In this model nonbonded interactions in the transition state are minimized by placing the metal enolate, in this case the metal aza-enolate aggregate, in the vacant region near the oxaziridine oxygen and nitrogen atoms and away from the sulfonyl group. The absolute configuration of (+)-**2a** was established by comparison with (2*S*,3*S*)-(+)-*N*-benzoyl-3-phenylisoserine methyl ester (**4**).[15] Reduction of (+)-**4** with lithium aluminum hydride (LAH) afforded 3(*S*)-(−)-(*N*-benzoylamino)-2(*S*)-

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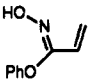
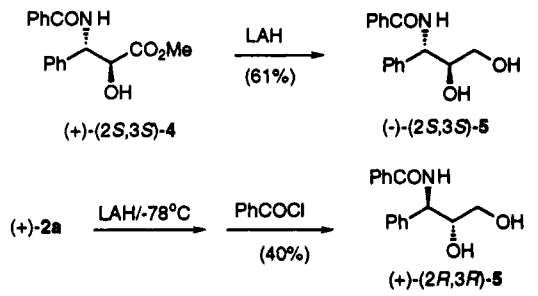
Table I. Hydroxylation of Dihydroisoxazole (DHI) Anions in THF at −78 °C

entry	DHI 1	oxaziridine 3	conditions[a] base/additive	4-isoxazolol (2) % yield[b]	4-isoxazolol (2) % ee[c] (config)
1	1a (R^1 = Ph, R^2 = H)	(+)-3a	LDA/TMEDA	50	7
2			LDA/B(OMe)$_3$/HMPA	59	0
3		(+)-3b	LDA	51	50 (+)-(*R*)
4			LDA/HMPA	41	56 (+)-(*R*)
3			LDA/TMEDA	52	58 (+)-(*R*)
4			LDA/B(OMe)$_3$/HMPA	43	22
5			LDA/LiCl/TMEDA	54	53
6		(+)-3c	LDA/TMEDA	49	30
7	1b (R^1 = PhS, R^2 = H)	(+)-3a	LDA/TMEDA	49	50 (−)-(*R*)
8		(+)-3b	LDA/TMEDA	56	31
9		(+)-3c	LDA/TMEDA	30	71 (−)-(*R*)
10	1c (R^1 = $PhSO_2$, R^2 = H)	(+)-3a	LDA/TMEDA	decomposition	
11	1d (R^1 = PhO, R^2 = H)	(+)-3a	LDA/TMEDA	65	
12	1e (R^1 = Ph, R^2 = *n*-Bu)	(+)-3a	LDA/TMEDA	85 (>95:5)	
13	1f (R^1 = Ph, R^2 = C_4H_8)	(+)-3a	LDA/TMEDA	no reaction	
14			LDA/HMPA	65	26 (−)-(*R*)

hydroxy-3-phenylpropanol (5) in 61% isolated yield. Similar reduction of (+)-2a (58% ee) at −78 °C with LAH followed by N-benzoylation of the resulting amino group gave (+)-5 in 40% yield and 50% ee having spectral properties (^{1}H NMR, IR) identical to those of (−)-5 but having the *opposite sign* of rotation. Since LAH is reported to reduce 1a to the *erythro* aminodiol by introduction of the hydride ion *syn* to the hydroxyl group,[16] (+)-2a must have the predicted *R* configuration. At higher temperatures greater racemization was observed in the reduction of (+)-2a, e.g., 34% ee at 0 °C.



The ee values for the 4-isoxazolols, summarized in Table I, are modest, reaching a high of 71% in the reaction of 3-phenylthio DHI 2b and (+)-[(3,3-dimethoxycamphoryl)-sulfonyl]oxaziridine (3c). The modest chiral induction probably reflects the lack of significant steric differentiation of *si* and *re* faces of the aza-enolates. Such differentiation is a prerequisite for high molecular recognition with the *N*-sulfonyloxaziridine asymmetric oxidizing reagents.[1,8]

The yields using oxaziridines 3 for the hydroxylation of DHI anions are comparable and in several cases better than Jäger's borate/oxidation method. The highest yields were observed for the 5-substituted DHIs 1e and 1f (65–85%; entries 12 and 13). In the former example it is noteworthy that only a single hydroxy diastereomer, *trans*-2e, was detected.

In summary, enantiomerically enriched 4-isoxazolols 2 are available in good yield by hydroxylation of the aza-enolates of DHIs with *N*-sulfonyloxaziridines 3. This method is recommended over other oxidation methods because of its efficiency and avoidance of toxic HMPA.

Experimental Section

Details concerning the recording of spectra, the analytical instruments used, the determination of melting points, elemental analyses, and the purification of solvents (freshly distilled) have been previously reported.[2a,14] LDA (1 mmol/mL) was prepared by treatment of 1.4 mL of diisopropylamine in 4.6 mL of THF by addition of 4.0 mL of 2.5 M *n*-butyllithium (Aldrich) at 0 °C. All reactions were performed under an argon/nitrogen atmosphere. Lithium chloride was dried in a vacuum oven at 120 °C/2 mm for 12 h. *N*-Hydroxybenzenecarboximidoyl chloride, used in the preparation of DHIs 1a, 1e, and 1f, was prepared by NCS chlorination of benzaldoxime.[17] The DHI 1b was prepared from 3-nitro-4,5-dihydroisoxazole by a published procedure and was oxidized to DHI 1c using *m*-CPBA.[18] (Camphorylsulfonyl)-oxaziridine derivatives 3a,[19] 3b,[14] and 3c[20] were prepared as previously described.

Preparation of DHIs 1a and 1e. The published procedures[21] were followed except that CH_2Cl_2 was used in place of ether and reaction was conducted at room temperature. DHI 1a: mp 66–68 °C (lit.[21] mp 66–67 °C). DHI 1e: mp 42.5–44 °C (lit.[21] mp 36–38.5 °C).

Preparation of DHI 1f. The procedure[21] used for preparation of 1e was followed except that methylenecyclopentane was used in place of 1-hexene. DHI 1f: mp 78.5–80 °C (lit.[22] mp 79.5–80 °C).

Preparation of 4,5-Dihydro-3-phenoxyisoxazole (1d). Aqueous NaOH (1.03 g in 20 mL; 25.6 mmol) was added to a stirred solution containing 3-nitro-4,5-dihydroisoxazole (1.11 g, 9.55 mmol) and phenol (2.82 g; 30 mmol) in THF (10 mL). The resulting mixture was stirred for 24 h and water (20 mL) and CH_2Cl_2 (20 mL) were added. The layers were separated and the aqueous layer was extracted with more CH_2Cl_2 (two 20-mL portions). The combined organic layers were washed with aqueous 5% NaOH (two 20-mL portions) and water (10 mL) and were dried over anhydrous Na_2SO_4. Concentration afforded an oil which slowly crystallized. Recrystallization from aqueous

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ethanol afforded 0.68 g (44% yield) of **1d**: mp 40.5–41.5 °C; IR (KBr) 1628 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.17 (t, 2H, J = 9.7 Hz), 4.50 (t, 2H, J = 9.7 Hz), 7.2–7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 33.1, 69.5, 119.8, 125.2, 129.3, 153.8, 166.9; mass spectrum, m/z 163 (M^+). Anal. Calcd for $C_9H_9NO_2$: C, 66.24; H, 5.56; N, 8.59. Found: C, 66.29; H, 5.70; N, 8.49.

(*R*)-(+)-4,5-Dihydro-3-phenyl-4-isoxazolol (2a). Typical Procedure. In a 50-mL round-bottom flask fitted with magnetic stir bar, argon inlet, and a rubber septum was placed 2.4 mL (2.4 mmol, 1.2 equiv) of freshly prepared lithium diisopropylamide (LDA) in THF. The reaction mixture was cooled to −78 °C in a dry ice–acetone bath, and 0.36 mL (2.4 mmol) of TMEDA and 0.294 g (2.0 mmol) of 4,5-dihydro-3-phenylisoxazole (**1a**) in 5 mL of THF were added. The dark yellow solution was stirred for 1 h at this temperature and a solution of 0.713 g (2.4 mmol) (+)-[(8,8-dichlorocamphoryl)sulfonyl]oxaziridine (**3c**) in 4 mL of THF was added dropwise and stirring continued for 1.5 h. The reaction mixture was quenched by addition of 2.0 mL of saturated NH_4Cl solution at −78 °C and warming to rt, and 50 mL of ethyl acetate was added. The organic portion was washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, and filtered. Removal of the solvent in vacuo afforded a solid which was redissolved in 30 mL of ether, filtered, and concentrated to give a solid which was purified by silica gel preparative TLC (1:1:3 ether:CH_2Cl_2:*n*-hexane) to give 0.152 g (48% yield) of (*R*)-(+)-**2a**: mp 95–96 °C (lit.[4] mp 96 °C); 58% ee, $[\alpha]^{20}_D$ +83.4° (*c* 1.63, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.40 (t, 1H, OH, exchangeable with D_2O), 4.23–4.61 (m, 2H), 5.34–5.63 (m, 1H), 7.29–7.63 (m, 3H), 7.72–7.96 (m, 2H).

Preparation of the Mosher Ester of 4-Isoxazolols. In a 25-mL round-bottom flask fitted with magnetic stir bar, argon inlet, and rubber septum was placed 0.1 mmol of the appropriate 4-isoxazolol **2** in 2 mL of dry CH_2Cl_2. The Mosher acid (0.046 g, 0.2 mmol, 2.0 equiv), 0.041 g (0.2 mmol) of dicyclohexylcarbodiimide (DCC), and a catalytic amount of 4-(dimethylamino)-pyridine (DMAP) were added, and the reaction mixture was stirred at rt for 2 days. On completion, as indicated by TLC, the solution was filtered, the solvent was removed under reduced pressure, and the Mosher ester was purified by silica gel preparative TLC (1:1:8 ether:CH_2Cl_2:*n*-pentane).

(*R*)-(−)-4,5-Dihydro-3-(phenylthio)-4-isoxazolol (2b). The preparation was similar to **2a**. Isolated in 56% yield was 4-isoxazolol **2b**: mp 79–80 °C; 71% ee, $[\alpha]^{20}_D$ −82.0° (*c* 1.6, $CHCl_3$); IR (KBr) 3433 (OH); 1633.3 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.54–2.62 (d, 1H, OH, exchangeable with D_2O), 4.19–4.40 (m, 2H), 4.87–5.00 (m, 1H), 7.33–7.43 (m, 3H), 7.53–7.64 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 76.0, 78.17, 128.1, 129.3, 129.5, 133.5, 158.3; mass spectrum, m/z (rel intensity) 195 (M^+, 51), 151 (23.6), 136 (34.8), 121 (8 0.9), 109 (100), 77 (64.5), 69 (60.2), 65 (76.8). Anal. Calcd for $C_9H_9NO_2S$: C, 55.38; H, 4.61. Found: C, 55.25; H, 4.62.

5-Butyl-4,5-dihydro-3-phenyl-4-isoxazolol (2e). The preparation was similar to **2a**. Isolated in 85% yield was 4-isoxazolol **2e**: mp 65–66 °C; IR (KBr) 3266 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, 3H, J = 7.2 Hz), 1.25–1.66 (m, 6H), 2.57–2.60 (d, 1H, OH, exchangeable with D_2O), 4.47–4.50 (m, 1H), 5.11 (dd, 1H, J = 3.1 Hz; J = 9.3 Hz), 7.26–7.41 (m, 3H), 7.78–7.82 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.5, 27.4, 32.2, 81.4, 88.9, 126.8, 128.1, 128.7, 130.1, 157.3. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.23; H, 7.76; N, 6.39. Found: C, 71.38; H, 7.97; N, 6.24.

(*R*)-(−)-3-Phenyl-1-oxa-2-azaspiro[4.4]non-3-en-4-ol (2f). In a 50-mL round-bottom flask fitted with magnetic stir bar, argon inlet, and a rubber septum were placed 0.201 g (1.0 mmol) of DHI **1f** and 0.37 mL (2.0 mmol) of HMPA in 6 mL of THF. The reaction mixture was cooled to −78 °C in a dry ice–acetone bath, 1.5 mL (1.5 mmol) of freshly prepared LDA in THF was added, and the dark red solution was stirred for 1 h. At this time 0.485 g (2.0 mmol) of (+)-(camphorylsulfonyl)oxaziridine (**3a**) in 5 mL of THF was added dropwise at −78 °C, the reaction mixture stirred for 2 h, and the reaction was quenched at this temperature by addition of 2.0 mL of saturated NH_4Cl solution. On warming to rt 35 mL of ethyl acetate was added, and the organic layer washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, and filtered. Removal of the solvent gave a solid which was dissolved in 30 mL of ether and filtered, and the solvent was removed, and the residue was purified by silica gel preparative TLC (1:1:8 ether:CH_2Cl_2:hexane) to give 0.143 g (65% yield) of (−)-**2f**: mp 172–175 °C; $[\alpha]^{20}_D$ −6.73° (*c* 1.1, MeOH); IR (KBr) 3431 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60–2.37 (m, 8H), 4.89 (d, 1H, J = 10.3 Hz), 7.35–7.46 (m, 3H), 7.76–7.89 (m, 2H); ^{13}C NMR (C DCl_3, CD_3OD) δ 23.9, 24.4, 28.9, 38.1, 80.0, 97.8, 126.6, 128.4, 128.9, 129.7, 158.8; mass spectrum, m/z (rel intensity) 217 (M^+, 86.7) 183 (54.4), 133 (100), 129 (41.64), 117 (32.8), 105 (32.8), 104 (76.1), 103 (36.3), 101 (51.5), 98, 97 (46.6), and 77 (67.2). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.97; N, 6.44. Found: C, 71.58; H, 7.17; N, 6.65.

Phenyl *N*-Hydroxy-2-propenimidate. The crude compound was purified by silica gel preparative TLC (15:85 ethyl acetate: *n*-pentane) to afford 0.062 g (65% yield) of phenyl *N*-hydroxy-2-propenimidate: mp 96–97 °C; IR (KBr) 3278 (OH), 1314, 1204, 1013, 752, and 668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.66–5.71 (d, 1H), 6.10–6.17 (d, 1H), 6.84–6.96 (m, 1H), 7.08–7.19 (m, 3H), 7.32–7.38 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 120.3, 120.5, 123.6, 124.7, 129.4, 153.7, 159.6; mass spectrum, m/z (rel intensity) 163 (M^+, 17.8), 95 (70), 94 (100), 91 (13.8). A satisfactory elemental analysis could not be obtained.

3(*R*)-(+)-(*N*-Benzoylamino)-2(*R*)-hydroxy-3-phenylpropanol (5) from (+)-2a. In a 50-mL round-bottomed flask equipped with a magnetic stir bar, rubber septum, and an argon inlet was placed 0.081 g (0.5 mmol) of (+)-(*R*)-4,5-dihydro-3-phenyl-4-isoxazolol (**2a**) in 3 mL of dry THF, and the solution was cooled to −78 °C. A 1 M solution of LAH in THF (1.0 mL, 1.0 mmol) was added dropwise at −78 °C, and the mixture was slowly allowed to warm to 0 °C over a 4-h period. The mixture was cooled to −78 °C, 1.0 mL of 10% aqueous Na_2SO_4 solution was added, and the reaction mixture was warmed to rt. The reaction mixture was diluted with 20 mL of ether and filtered through Celite. An additional 10 mL of ether was used to wash the Celite. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was diluted with 3 mL of CH_2Cl_2 and added dropwise to a mixture of 0.105 g (0.75 mmol) of benzoyl chloride in 2 mL of CH_2Cl_2 and 1.5 mL of 10% $NaHCO_3$ solution at 0 °C. The reaction mixture was stirred for 8 h at 0 °C, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude material was purified twice by preparative TLC (30:70 acetone:CH_2Cl_2) to give 0.022 g (40% yield) of (+)-(2*R*,3*R*)-**5**: mp 158–159 °C; $[\alpha]^{20}_D$ +8.09° (*c* 0.63, MeOH); IR (KBr) 3312 (OH), 1636 (NHCOPh) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.14 (br s, 2H, 2OH, exchangeable with D_2O), 3.69–3.73 (m, 1H), 3.90–4.05 (m, 1H), 5.23–5.29 (m, 1H), 7.14 (d, NH, exchangeable with D_2O), 7.31–7.54 (m, 8H), 7.76 (d, 2H); ^{13}C NMR ($CDCl_3$) δ 5 6.65, 63.08, 73.59, 126.90, 127.30, 128.04, 128.50, 128.90, 131.80, 167.70; mass spectrum, m/z (rel intensity) 271 (M^+, 26.3), 253 (M^+ − 18, 1.9), 210 (84.4), 122 (14.9), 105 (100), 91 (24.3), 77 (87.5). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.84; H, 6.27; N, 5.16. Found: C, 70.74; H, 6.48; N, 5.23.

3(*S*)-(−)-(*N*-Benzoylamino)-2(*S*)-hydroxy-3-phenylpropanol (5) from (+)-4. In a 25-mL round-bottomed flask equipped with a magnetic stir bar, rubber septum, and argon inlet was placed 0.015 g (0.05 mmol) of (+)-(2*S*,3*S*)-*N*-benzoyl-3-phenylisoserine methyl ester (**4**)[15] in 2 mL of dry THF and the solution cooled to 0 °C. A 1 M solution of LAH in ether (0.1 mL; 0.1 mmol) was added dropwise, and the mixture was stirred for 4 h and quenched by addition of 0.5 mL of a 10% Na_2SO_4 solution. After the solution was warmed to rt, 20 mL of ethyl acetate was added and the mixture filtered through Celite. The Celite was washed carefully with an additional 10 mL of ethyl acetate. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude material was purified by preparative TLC (30:70 acetone:CH_2Cl_2) to afford 0.008 g (61%) of (−)-**5**: $[\alpha]^{20}_D$ −16.3° (*c* 0.52, MeOH); spectral properties were identical to those of (+)-**5**.

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