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Asymmetric Nitrone-Vinyl Sulfoxide Cycloadditions: a Highly Enantioselective Synthesis of (+)-Sedridine

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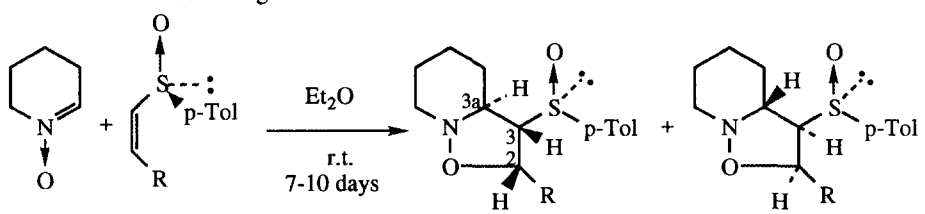
Abstract: Cycloaddition of 2,3,4,5-tetrahydropyridine-1-oxide **1** to (Z)-(*R*)-vinyl sulfoxides **2***a-d* proceeds in high yield to give isoxazolidines **3***a-d* and **4***a-d* with complete *exo* selectivity and with 82-98% asymmetric induction. This method provides an efficient synthesis of the enantiomerically pure piperidine alkaloid (+)-sedridine **6***a*.

1,3-dipolar cycloaddition of nitrones to alkenes has been widely utilized for the synthesis of many nitrogen containing natural products. Indeed, in this process, up to three stereogenic centers are built up in a single step, often in a highly stereoselective manner. The thus obtained isoxazolidines are versatile synthons and can be converted into a variety of compounds with complete control of the stereochemistry[1].

Recently, much attention has been paid to asymmetric nitrone-alkene cycloadditions involving either chiral nitrones[2] or chiral alkenes[3] or chiral catalysts[4]. In the context of our ongoing interest in the use of chiral α,β-unsaturated sulfoxides as dipolarophiles[5], we wish to report on the high diastereoselectivity observed in the cycloaddition of nitrone **1** onto vinyl sulfoxides **2***a-d*.

(Z)-(R)-vinyl sulfoxides **2***a-d* were prepared according to literature procedures[6]. Cycloaddition of 2,3,4,5-tetrahydropyridine-1-oxide **1** (3-5 equiv.) to (Z)-(R)-vinyl sulfoxides **2***a-d* (1 equiv.) in ether proceeded at room temperature for 7-10 days to give a mixture of isoxazolidines **3***a-d*, **4***a-d* along with unreacted starting materials[12] (Scheme 1). As it can be seen from the results summarized in Table 1, yields and diastereomeric ratios are high.



1 **2***a-d* **3***a-d* **4***a-d*

Scheme 1

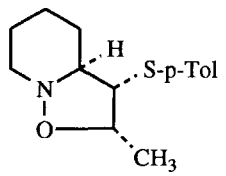
Isoxazolidines **3***a* and **4***a* yielded enantiomeric sulfides **5***a* after TMSI/NaI reduction (Figure 1), indicating that both cycloadducts possess the same relative configuration at C3a, C3 and C2. Hence they are diastereomeric due to the sulfoxide chirality and the **3***a-d* /**4***a-d* ratios presented in Table 1 reflect the degree of asymmetric induction during the cycloaddition process. Relative and absolute configurations of

isoxazolidines ***3a-d*** were established by their conversion into known optically active compounds (*vide infra*). Both diastereomers arise from an *exo* transition state (H3a,H2 *trans*).

Table 1. Nitrone Cycloaddition to (Z)-(R)-Vinyl Sulfoxides

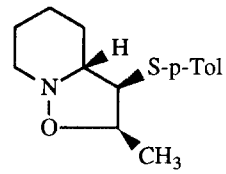
Entry	Sulfoxide	R	Yield[a](%)	3 / 4	$[\alpha]_D^{22}$[d] 3	c
1	**2*a***	CH_3	95	94 : 6[b] (91 : 9)[c]	+219	1.3
2	**2*b***	*n*-C_3H_7	90	95 : 5[b] (93 : 7)[c]	+190	1.2
3	**2*c***	*n*-C_5H_{11}	85	95 : 5[b] (93 : 7)[c]	+175	1.1
4	**2*d***	C_6H_5	97	99 : 1[b] (> 98 : 2)[c]	+50	1.1

[a]Isolated Yields; [b]Isolated ratios; [c]Determined by ^1H NMR on the crude reaction product; [d]Measured for solutions in $CHCl_3$



(-)-5*a*

$[\alpha]_D^{22}$-58 ($CHCl_3$; c=0.4)

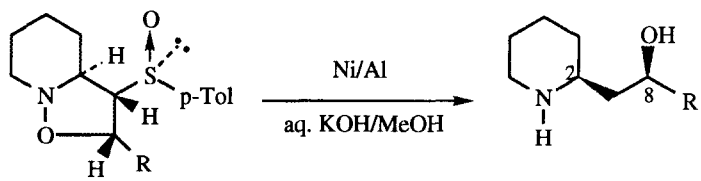


(+)-5*a*

$[\alpha]_D^{22}$+56 ($CHCl_3$; c=0.8)

Figure 1

Hydrogenolysis of the major cycloadducts ***3a-c*** using Ni/Al alloy afforded desulfurized 1,3-amino alcohols ***6a-c*** in quite modest yields (Scheme 2). The results are summarized in Table 2 and deserve some comments.



3a-d ***6a-d***

Scheme 2

Table 2. Reductive Cleavage of Isoxazolidines **3** using Ni/Al alloy

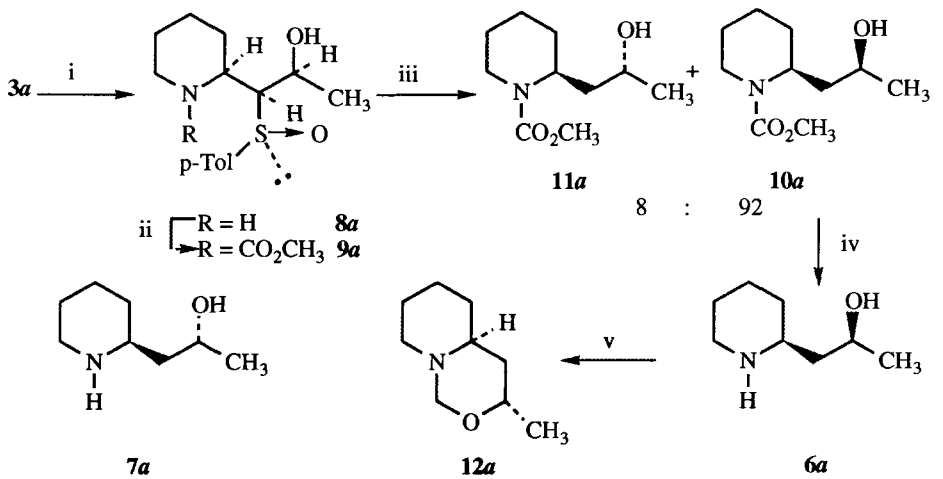
Entry	Isoxazolidine	Amino alcohol	Yield (%)	$[\alpha]_D^{22}$[b] **6**	c	$[\alpha]_D^{22}$[b] **6** lit.	c	Ref
1	**3*a***	**6*a***[a]	37	+23	1.1	+28.5	2.32	3c
2	**3*b***	**6*b***	60	+17	0.4	+19.6	0.6	8
3	**3*c***	**6*c***	43	+9	0.7			
4	**3*d***	**6*d***	0					

[a]Isolated as a 95 : 5 mixture of **6*a*** /**7*a***; [b]Measured for solutions in EtOH

(+)-Sedridine **6*a*** [7] and (-)-halosaline **ent-6*b*** [8] are natural piperidine alkaloids isolated from *Sedum acre* and *Haloxylon salicornicum* respectively. Relative and absolute configurations of the dextrorotatory bases were unambiguously determined as (2*S*,8*S*). Therefore we assign the homologous dextrorotatory amino alcohol **6*c*** the same (2*S*, 8*S*) configuration from the sign of the specific rotation and from the similar chromatographic behaviour of the diastereomeric isoxazolidines throughout the series.

Attempted reduction / desulfurization of isoxazolidine **3*d*** under the same conditions yielded a complex mixture, the amino alcohol (+)-norallosedamine **6*d*** being undetected. Benzylic alcohols have already been reported to undergo various reactions in the presence of Ni/Al alloy[9]. Treatment of cycloadduct **3*a*** with Ni/Al gave (+)-sedridine **6*a*** accompanied by 5% allosedridine **7*a***. This finding along with the low value of the specific rotation of **6*b*** suggest that some epimerization and/or racemization occurred during the reductive desulfurization process[10]. To overcome this problem, isoxazolidine **3*a*** was first reduced with a slight excess of Ni/Al alloy to the amino alcohol **8*a*** in 93% yield (Scheme 3). W6 Raney Nickel[11] desulfurization (in the presence of hydrogen) of N-protected amino alcohol **9*a*** afforded (2*S*,8*S*)-N-carbomethoxysedridine **10*a*** and (2*S*,8*R*)-N-carbomethoxyallosedridine **11*a*** in 84% yield and in a 92:8 ratio.

Deprotection of **10*a*** gave enantiomerically pure (+)-sedridine {$[\alpha]_D^{22}$ +26 (EtOH; c=1.3)} in 97% yield.



Reagents and conditions : i : Ni/Al (3x weight), aq. KOH 1M/MeOH, r.t., 2h. (93%); ii: $ClCO_2CH_3$ (10 equiv.), aq. K_2CO_3, r.t., overnight (98%); iii: W6 Raney Nickel/H_2, MeOH, overnight (84%); iv: (a) TMSI, CH_2Cl_2, reflux, 1h. (b) MeOH, r.t., 10 min (97%); v: CH_2O, MeOH, r.t., 15 min (83%)

Scheme 3

In order to determine its e.e., **6*a*** was converted into **12*a*** by treatment with formaldehyde in methanol. The e.e. of **12*a*** was proved to be more than 96% by use of the chiral NMR shift reagent Eu(hfc)$_3$. The new highly diastereoselective nitrone cycloaddition described above provides an efficient synthesis of enantiomerically pure (+)-sedridine (62% overall yield from **2*a***). Further study of this reaction and its application to the asymmetric synthesis of nitrogen containing target molecules is in progress and will be reported in due course.

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12. The structures of all new compounds were supported by satisfactory ^{1}H NMR, ^{13}C NMR and High Resolution Mass Spectral analyses except for **4*b***, **4*c*** and **4*d*** (^{1}H NMR and High Resolution M.S. only).

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