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Diastereoselective Reduction of Chiral *N*-Tosyl 2-Benzoyl-1,3-oxazines Derived from D-Glucose

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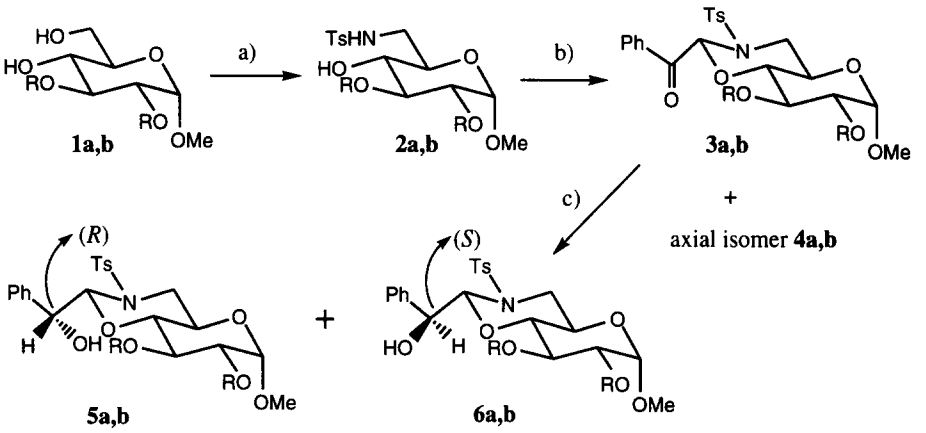
Abstract: Stereochemistry of reduction of the diastereomerically pure *N*-tosyl 2-benzoyl-1,3-oxazines prepared from D-glucose was investigated with various reducing agents. It was found that the stereochemical outcome is consistent with the Cram's chelation model where the ring oxygen atom is involved in chelation, not the tosyl oxygen as in the 5-membered oxazolidines.

The diastereoselective addition of nucleophilic reagents to chiral 2-acyl-1,3-oxazolidines derived from enantiomerically pure β-aminoalcohols is used for the preparation of α-hydroxy carbonyl derivatives.[1] Because the *N,O*-acetal functionality is easily hydrolyzed, the amino group is usually protected with tosyl or Boc group.[2] As an example, reduction of a norephedrine-derived *N*-tosyl 2-acetyloxazolidine with tri-*sec*-butylborohydrides in the presence of metal halides gave the chelation product in high selectivity, which was explained to be the result of a hydride addition on an intermediate involving a chelation between the carbonyl group and the sulfonyl group (not the ring oxygen atom).[1a] Similarly, chelation involving the carbonyl oxygen atom of *t*-Boc group was observed in the addition of organometallic reagents to *N*-Boc 2-acyl-1,3-oxazolines.[1c]

Recently, Eliel and coworkers reported that addition of Grignard, organolithium reagents, and hydride reducing agents to *N*-benzyl 2-acyl-1,3-oxazines derived from (+)-pulegone proceed in high stereoselectivity according to Cram's chelate rule involving the ring oxygen atom.[3] However, stereochemistry of nucleophilic addition to the chiral 2-acyl-1,3-oxazines have been less studied than 1,3-oxazolidines, presumably because optically pure 1,3-aminoalcohols are less easily available than β-aminoalcohols.[4] In order to determine whether the sulfonamide group takes part in chelation during nucleophilic addition to *N*-tosyl 2-acyl-1,3-oxazines, as in the case of 5-membered analogs, we prepared chiral 3-*N*-tosyl 2-benzoyl-1,3-oxazines as model compounds, starting from D-glucose[5] and investigated the diastereoselective reduction.

Scheme 1 shows a preparation of phenyl ketone **3a**.[6] Functional group interconversion of the hydroxyl group of known diol **1a**[7] gave the *N*-tosylamino alcohol **2a** in 51% overall yield, which upon condensation with phenylglyoxal hydrate was converted to a mixture of equatorial ketone **3a** and axial ketone **4a** in a ratio of 3 : 1 (65% purified yield). Fortunately, ketones **3a** and **4a** were easily separated by chromatography on silica gel (EtOAc/hexanes 1:1) (R_f of **3a** = 0.20; R_f of **4a** = 0.35). Similarly, condensation of 2,3-*O*-dipivaloyl derivative **2b**, obtained from diol **1b**[8] in 65% overall yield with phenylglyoxal hydrate gave a separable mixture of equatorial ketone **3b** (R_f = 0.18 in EtOAc/hexanes 1:4) and axial ketone **4b** (R_f = 0.27) in a ratio of 3 : 1 (59% purified yield).

a series: R = Me; b series: R = pivaloyl (Purified yields are shown in the order of a and b series.)



a) TsCl, pyridine, rt, 24 hr, 80%, 86%; NaN_3, DMF, 80-85 °C, 10 hr, 89%, 90%; H_2, 10% Pd/C, EtOH, 89%, 93%; TsCl, K_2CO_3, H_2O-CH_2Cl_2, rt, 7 hr, 80%, 91%. b) phenylglyoxal hydrate, TsOH, benzene, reflux, 20 hr, 65%, 59%. c) column separation; reducing agents

Scheme 1

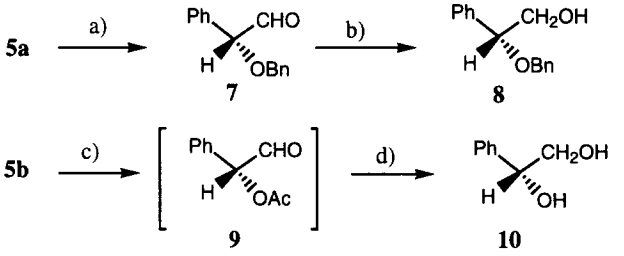
The diastereoselectivity in the reduction is shown in Table 1. Whereas chelating agents such as $LiAlH_4$ (entries 2 and 3) and L-Selectride®(entries 4 and 5) showed excellent selectivity (>98%) at the reduction of ketone **3a**, non-chelating agents such as dibal or *n*-Bu_4NBH_4 showed modest selectivity. However, the major product was the (*R*)-isomer in both cases. The reduction of ketone **3b** having *O*-pivaloyl protective groups was less selective than that of ketone **3a**.

Table 1. Diastereoselectivity in the Reduction of *N*-Tosyl 2-benzoyl-1,3-oxazines **3a,b**[a)]

entry	reagent	solvent	temp. (°C)	de (%)[b)]	de (%)[c)]
1	$NaBH_4$	EtOH	0	70 (83)	68 (89)
2	$LiAlH_4$	THF	-78	98 (83)	30 (95)
3	$LiAlH_4$	ether	-78	98 (87)	d)
4	L-Selectride®	THF	-78	98 (92)	0 (98)
4a	L-Selectride®/12-crown-4[e)]	THF	-78	40 (85)	f)
5	L-Selectride®	ether	-78	98 (90)	0 (92)
5a	L-Selectride®/12-crown-4[e)]	ether	-78	50 (92)	f)
6	$LiAlH(O\text{-}t\text{-}Bu)_3$	THF	-78	0 (83)	64 (90)
6a	$LiAlH(O\text{-}t\text{-}Bu)_3$/12-crown-4[e)]	THF	-78	f)	52 (90)
7	$LiAlH(O\text{-}t\text{-}Bu)_3$	ether	-78	0 (85)	50 (95)
8	*n*-Bu_4NBH_4	CH_2Cl_2	20	78 (98)	54 (96)
9	dibal	toluene	-78	60 (94)	d)

[a)] Determined by ^1H NMR on the crude products. [b)] Ketone **3a**. Yields (%) are shown in the parenthesis. [c)] Ketone **3b**. Yields (%) are shown in the parenthesis. [d)] Protecting groups were decomposed. [e)] Molar ratio of ketone, reducing agent, and crown ether = 1 : 3 : 5. f) Not determined.

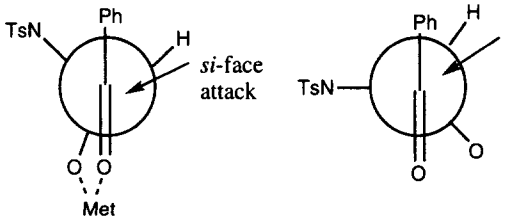
The absolute configuration of the newly formed carbinol center was determined as shown in Scheme 2. Benzylation of carbinol **5a** (de 70%) from $NaBH_4$ reduction followed by acidic hydrolysis (5 % HCl/EtOH 1 :5, reflux, 12 hr) gave 2-benzyloxy aldehyde **7**, which was reduced with $NaBH_4$ to alcohol **8** (69% overall yield), $[\alpha]_D^{20}$ -62.4 (c = 1.80, $CHCl_3$) [in lit.[9] for the (*R*)-isomer of unknown optical purity, $[\alpha]_D$ -53.9 (c = 1.50, $CHCl_3$)]. In the case of carbinol **5b**, acetylation of the alcohol (de 68%) obtained from $NaBH_4$ reduction followed by acidic hydrolysis (5 % HCl/EtOH 1:5, reflux, 12 hr) gave the crude aldehyde **9**, which without further purification was reduced with $LiAlH_4$ in ether to diol **10** (61% overall yield), $[\alpha]_D^{20}$ -43.0 (c = 0.85, $CHCl_3$) [in lit.[10] for the (*R*)-isomer, $[\alpha]_D^{20}$ -69 (c = 1, $CHCl_3$)]. The enantiomeric excess of this diol, determined by the chiral shift reagent method[11] was found to be 70% ee, which agreed very well with the precursor de value. Thus, in both cases, the major carbinol has the (*R*)-configuration.



a) BnBr, NaH, THF, 76%; HCl, H_2O-EtOH, reflux, 96%. b) $NaBH_4$, EtOH, 94%. c) Ac_2O, DMAP, pyridine, 92%; HCl, H_2O-EtOH, reflux. d) $LiAlH_4$, ether, 66%.

Scheme 2

This stereochemistry is consistent with either chelation model **A** involving the ring oxygen (not the *N*-tosyl group) or Felkin-Anh model **B** where the highly electronegative tosylamino group occupies the position of the largest substituent in transition state.[1b] However, in the light of decreased selectivity in the presence of crown ether (entries 4 vs. 4a, 5 vs. 5a, and 6 vs. 6a) and the higher selectivity of chelating agents compared to non-chelating agents as shown in Table 1, the chelating reducing agent may react in a chelation-controlled manner. On the other hand, non-chelating agents such as *n*-Bu_4NBH_4 and dibal seem to prefer to react according to a Felkin-Anh model **B**.[1b] Worse selectivity shown by pivaloyl protective group can be explained by assuming that the bulky pivaloyl groups block the hydride attack on the *si*-face of ketone in either model.



A: Chelation Model **B**: Felkin-Anh Model

The present study suggests that the reduction of 3-*N*-tosyl 2-benzoyl-1,3-oxazines derived from D-glucose with chelating agents proceeds through chelation mode involving the ring oxygen atom. This result is

in a sharp contrast with the case of 5-membered analog, where *N*-tosyl group rather than the ring oxygen is involved in a chelation.[1a]

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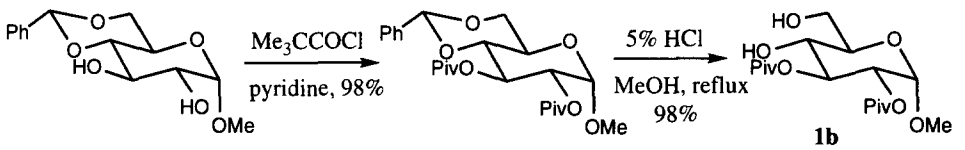

1b

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