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TELLURIUM: USE IN THE SYNTHESIS OF ALLYLIC AMINES FROM 5-HYDROXYMETHYL-2-OXAZOLIDINONES

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Summary: Non-racemic or racemic allylic amines are obtained by treatment of sulfonate esters of 5-hydroxymethyl-2-oxazolidinones with telluride ion.

Allylic amines have been cited as important synthetic intermediates and as components of drugs and natural products.[1] For example, oxidation of the carbon-carbon double bond yields either α- or ß-amino acids depending on conditions;[2] epoxidation has been used in the synthesis of hydroxyethylene peptide isosteres as protease inhibitors in AIDS therapy[3] and as renin inhibitors for regulation of blood pressure.[4] The allylic amine functionality has been used to provide a framework for peptide mimetics and isosteres and for ß-turn promoters.[5] Certain allylic amines are valuable intermediates in ring-closing metathesis reactions,[6] and as precusors of intermediates in the aza-Claisen rearrangement.[7]

Tellurium in its reduced form (Te^{2-}) is a versatile reagent for effecting nucleophilic reductions;[8] and the conversion of sulfonate esters of aziridinemethanols to allylic amines is a recent example [1f] of the process in which telluride ion is oxidized to its elemental form which precipitates and can be reused, while the organic substrate is formally reduced. The scope of our previous work with aziridines was restricted by the lack of availability of some aziridinemethanols, the poor regioselectivity of reactions of aziridinemethanol sulfonate esters with an electron-withdrawing group on the nitrogen atom, and the inability to prepare linalyl amine which has the amino group on an allylic tertiary carbon atom.[1f] Some recent examples of the preparation of allylic amines in addition to those previously cited[1a,b,f] include a non-racemic synthesis via sulfinimines,[9] and methods involving benzotriazole derivatives of α-amino acids,[1c] additions to imines,[10] and additions of lithiated amines to acetylenes.[11]

In a search for new candidates for a telluride-catalyzed nucleophilic reduction that would yield allylic amines, we examined sulfonate esters of 5-hydroxymethyl-2-oxazolidinones. A 5-iodomethyl derivative is reported to give an allylic amine when treated with metallic zinc.[12] Schemes 1 and 2 illustrate synthesis of non-racemic allylic amines via optically active aminodiols obtained from allylic alcohols via Sharpless asymmetric epoxidation[13] followed by selective ring opening with an amine.[14] (1*R*, 2*R*)-3-(*t*-Butyldiphenylsilyloxy)-1-phenyl-1-N-(*n*-hexylamino)-2-propanol **2** was prepared in 89% yield by addition of imidazole (1.74 g, 25.5 mmol) and TBDPSCl (2.81 g, 10.2 mmol) to a solution of aminodiol **1**(2.57 g, 10.2 mmol) in tetrahydrofuran (THF) (10 mL). After 5 h, the reaction was complete. Treatment of **2** with triphosgene and triethylamine in methylene chloride for 12 h at room temperature (rt) gave the oxazolidinone **3** in 92% yield. (4*R*, 5*R*)-3-(*n*-Hexyl)-5-(hydroxymethyl)-4-phenyloxazolidin-2-one **4a** was prepared by addition of tetra-*n*-butylammonium fluoride (TBAF) (4.62 mL, 4.62 mmol) to a solution of **3** (1.59 g, 3.08 mmol) in THF. The lower yield in this step is believed to be due to losses in chromatographic purification. The tosylation reaction of compound **4a** with p-toluenesulfonyl chloride (TsCl), triethylamine, and 4-(N,N-dimethylamino)pyridine (DMAP) in methylene chloride gave (4*R*, 5*R*)-3-(*n* -hexyl)-5-(4-methylbenzenesulfonyloxymethyl)-4-phenyloxazolidin-2-one **5a** (93% yield) which was treated with an aqueous solution of telluride ion for 24 h to give the allylic amine **6a** in 95% yield. An alternative method from aminodiol to allylic amine could involve conversion of the diol to a cyclic sulfate ester or to a dimesylate or dibromide followed by treatment with telluride ion.[15] These methods, however, might cause undesired reactions involving the amino function.

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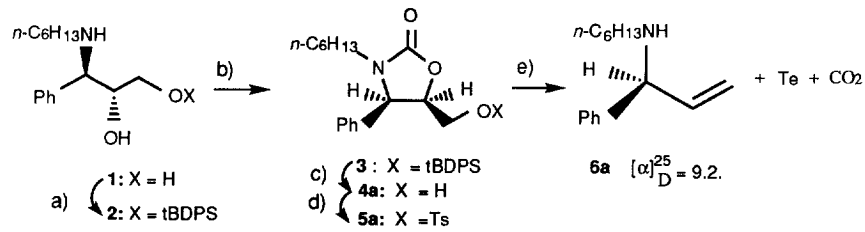
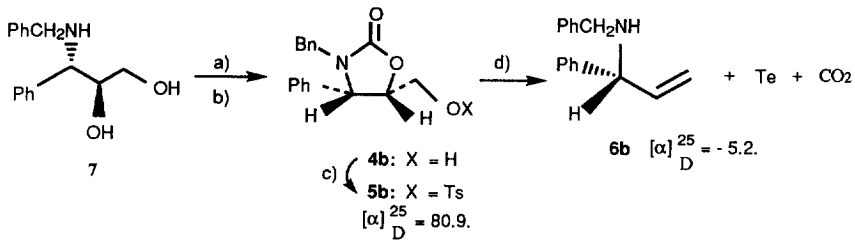
Scheme 1



a) tBDPSCl, imidazole, rt, THF, 5 h, 89%. b) $(Cl_3CO)_2C{=}O$, Et_3N, CH_2Cl_2, rt, 12 h, 92%. c) $Bu_4N^+F^-$, THF, rt, 3 h, 70%. d) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 2-3 h, 93%. e) Te + $NaBH_4$ + H_2O, Adogen 464, toluene, rt, 24 h, 95%.

Protection of the primary alcohol functionality with *t*-butyldiphenylchlorosilane as shown in Scheme 1 is necessary to avoid complications caused by its reaction with triphosgene. This protection and subsequent deprotection step can be avoided if the less reactive methyl chloroformate is used to form the oxazolidinone ring (Scheme 2). Aminodiol **7** was prepared according to the standard procedure.[14] The carbamate intermediate was prepared in 89% yield by stirring the mixture of aminodiol **7**, methyl chloroformate, and potassium carbonate in THF for 7 h.[17] The crude carbamate was disssolved in 10% methanolic potassium hydroxide (12 mL) to give 3-(*n*-benzyl)-5-(hydroxymethyl)-4-phenyloxazolidin-2-one **4b** in 85% yield. Tosylation of compound **4b** with TsCl, triethylamine, and DMAP in methylene chloride gave (4*R*, 5*S*)-3-(*n*-benzyl)-5-(4-methylbenzenesulfonyl-oxymethyl)-4-phenyloxazolidin-2-one **5b** (94% yield) which was then treated with an aqueous solution of telluride ion for 24 h to give the allylic amine **6b** in 84% yield. Both triphosgene[16] and chloroformate esters[17] are effective in the formation of oxazolidinones or their carbamate precursors, respectively.

Scheme 2



a) $ClCO_2Me$, rt, THF, K_2CO_3, 89%. b) KOH in 10% MeOH, rt, 3.5 h, 85%. c) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 2-3 h, 94%. d) Te + $NaBH_4$ + H_2O, Adogen 464, toluene, rt, 24 h, 84%.

The reduction of tellurium to telluride ion may be performed with a variety of reagents,[18] but the convenient phase transfer conditions work best for us with aqueous sodium borohydride.[19] Table 1 lists the allylic amines prepared by the telluride method.[20] Notable is **6d**, a linalyl amine,[21] which was not able to be obtained in our previous investigation on aziridines.[1f]

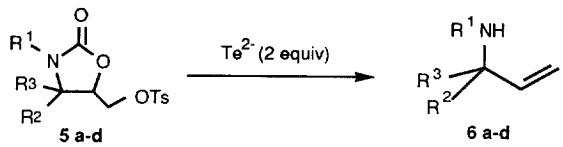
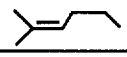


Table 1. Allylic Amines from 5-Hydroxymethyloxazolidinone Tosylates

6	R^1	R^2	R^3	6, % Yield
a	*n*-C_6H_{13}	Ph	H	95[a]
b[22]	$PhCH_2$	Ph	H	93
c	4-Methoxybenzyl	*n*-C_3H_7	H	66[b]
d	*n*-C_6H_{13}		Me	79

(a) The yield of the racemic product was 69%.

(b) The yield of this product was decreased due to losses in work-up.

These are the first reported reactions of telluride ion with 5-hydroxymethyl-2-oxazolidinone derivatives.[23] The usefulness of the method is that either enantiomer of a non-racemic allylic amine can be obtained since the starting enantiomeric oxiranemethanols are available via the Sharpless procedure.[13] The substituent on the nitrogen atom can be varied according to the amine used in the titanium alkoxide mediated ring opening of the oxiranemethanol.[14] The tellurium is not consumed. The reaction of the oxazolidinone derivatives, eg **5a**, **5b**, with telluride has excellent regioselectivity unlike that observed with some aziridinemethanol derivatives reported previously.[1f]

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20. Selected properties: **6a:** ^{1}H NMR ($CDCl_3$) δ 0.82 (t, J=7, 3H), 1.19-1.45 (m, 8H), 2.46 (m, 2H), 4.11 (d, J=7, 1H), 5.02 (dd, J=10, 1, 1H), 5.13 (dd, J=16, 1, 1H), 5.84 (m, 1H), 7.16-7.27 (m, ArH, 5H); ^{13}C NMR ($CDCl_3$) δ 143.23, 141.40, 129.56, 128.56, 114.82, 99.67, 66.41, 47.83, 31.80, 30.14, 27.10, 22.73, 14.18. **6b**: ^{1}H NMR ($CDCl_3$) δ 3.73 (d, J=15, 1H), 3.76 (d, J=15, 1H), 4.25 (d, J=7, 1H), 5.14 (dd, J= 12, 2, 1H), 5.25 (dd, J= 20, 2, 1H), 5.97 (m, 1H), 7.27-7.39 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 142,96, 141.13, 140.62, 129.02, 128.69, 128.53, 128.40, 127.11, 127.05, 115.28, 65.26, 51.44. **6c**: ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J=7, 3H), 1.27–1.50 (m, 4H), 3.00 (m, 1H), 3.61 (d, J=9, 1H), 3.75 (d, J=9, 1H), 3.81 (s, 3H), 5.10 (dd, J=15, 3, 1H), 5.15 (dd, J=9, 3, 1H), 5.60 (m, 1H), 6.86 (d, J=9, 2H), 7.23 (d, J=9, 2H); ^{13}C NMR ($CDCl_3$) δ 141.60, 133.01, 129.40, 126.95,115.89, 113.84, 61.0, 55.26, 50.72, 38.06, 19.19, 14.20. **6d**: ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J=7, 3H), 1.10 (s, 3H), 1.22-1.45 (m, 8H), 1.58 (s, 3H), 1.60 (s, 3H), 1.93 (m, 4H), 2.43 (m, 2H), 4.97-5.08 (m, 3H), 5.65 (dd, J=15,10, 1H); ^{13}C NMR ($CDCl_3$) δ 145.49, 124.67, 112.66, 99.67, 56.84, 54.24, 42.46, 40.17, 31.89, 30.10, 29.39, 27.2, 25.71, 23.35, 22.64, 14.10.
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23. *Experimental procedure*: A suspension of Te (0.51 g, 4 mmol) in water (12 mL) was heated (80 °C) under argon for 30 min. Sodium borohydride (10.8 mmol) in water (5 mL) was added to the hot suspension to rapidly obtain a purple solution of telluride ions (Te^{2-}_n). A mixture of the oxazolidinone tosylate (2.08 mmol) and the phase transfer catalyst Adogen 464 (0.1 g) in toluene (10 mL) was added to the aqueous telluride solution by syringe, and the reaction mixture was stirred for 24 h at room temperature. Toluene (50 mL) was added, and air was passed through the solution for 30 min to oxidize unreacted telluride ion to the element. After the black elemental Te had settled (about 1 hour), the organic layer was removed by a pipet; toluene extraction was repeated twice, and the combined toluene extracts were washed with concentrated aqueous sodium chloride, and dried ($MgSO_4$). Evaporation of the solvent gave crude allylic amine which may be purified by column chromatography (silica gel).