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Selective Reduction of C-C Double Bonds of 2-Vinylaziridnes: Preparation of Enationmerically Pure 2-Alkylaziridines

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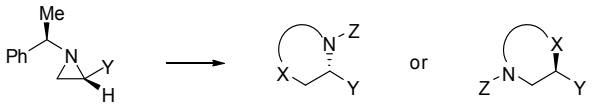
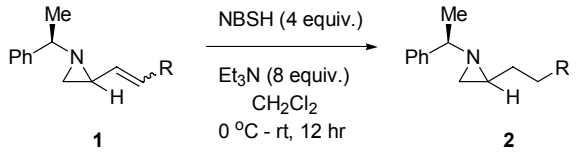
The synthetic utility of aziridine, nitrogen-containing thee membered ring, stems from the regio- and stereoselective ring-opening reactions with the proper side chains attached to the ring.[1] Since we have developed the preparation of enantiomerically pure N-α-methylbenzyl-(2R)- and (2S)-aziridine-2-carboxylates,[2] it is possible to achieve the asymmetric synthesis of diverse nitrogen-containing compounds including amino acids, amino alcohols, diamines, and many heterocycles *via* functional group transformation of carboxylates and aziridine ring openings (Scheme 1).[3]



Scheme 1

To enrich the utility of enantiomerically pure (2R)- and (2S)-aziridine-2-carboxylates, it is necessary to develop a proper method for the preparation of 2-alkylaziridine which has various functional group in the side chain. The substitution of 2-toluenesulfonyloxymethyaziridne with alkyl nucleophiles has been studied to result limited success.[4] Only one isomer 1-[1′(R)-α-methylbenzyl]-(2S)-(sulfonyloxymethyl) aziridines reacted with dialkylcuprates to give the expected alkylation products while the other isomer (2R)-(sulfonyloxymethyl) aziridine did not provide the coupling product. The conformational restriction of the bulky α-methylbenzyl group on the ring nitrogen seems to limit the accessibility of nucleophiles toward the reaction site. Another option to obtain 2-alkylaziridine is the selective reduction of vinylaziridines[5] which can be prepared from the olefination of 1-α-methylbenzyl-(2R)- and (2S)-aziridine-2-carboxyaldehyde. However, there are three potential reduction sites in the substrates including α-methylbenzyl group, allylic activated aziridine ring C(2)-N bond, and double bond in the side chain. Due to the high strain energy of the aziridine ring, it can be reduced by many reductive conditions.[6] Additional allylic activation by the double bond makes the ring much more vulnerable to reduction conditions.[7] Since there has been no report for the selective reduction of C-C double bonds of 2-vinylaziridines for the preparation of enatiomerically pure 2-alkylaziridines, we would like to describe the selective reduction method with its synthetic scopes.



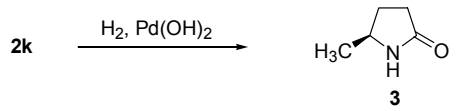
1 **2**

Entry	Configuration of C-2	R	Yield (%)
1	S(**1a**)	*n*-Pr (**2a**)	83
2	S(**1b**)	*n*-Hex (**2b**)	99
3	S(**1c**)	Dodecane (**2c**)	78
4	S(**1d**)	Ph (**2d**)	91
5	S(**1e**)	*p*-Tolyl (**2e**)	64
6	S(**1f**)	4-Cl-Ph (**2f**)	72
7	S(**1g**)	4-NO_2-Ph (**2g**)	71
8	S(**1h**)	2-I-Ph (**2h**)	95
9	S(**1i**)	2-F-4-Br-Ph (**2i**)	70
10	S(**1j**)	CN (**2j**)	78
11	S(**1k**)	COOEt (**2k**)	78
12	R(**1'a**)	*n*-Pr (**2'a**)	82
13	R(**1'b**)	Ph (**2'b**)	83

Scheme 2

At first hydrogenation methods were applied with various transition metal catalysts including Pd, Pt, and Rh for the selective reduction of the olefin in the 2-vinylaziridine substrate to yield the aziridine C(2)-N bond reduced products due to the formation of π-allyl complex in all cases.[8] Then we looked into reduction conditions without using transition metals and found that diimide would be a suitable reagent for the selective reduction of the double bond without reducing ring C(2)-N bond. Since the aziridine is very labile in acidic condition to give the corresponding ring opening product we used decomposition of arylsulfonylhydrazine in the presence of a base to generate diimide.[9] Using arylsulfonylhydrazine provided a promising result to yield the expected double bond reduction product in less than 50% yield with some decomposition products due to harsh reaction condition. However, *o*-nitrobenzene-sulfonyl-hydrazide (NBSH) was known for a convenient precursor of diimide since the *o*-nitrobenzene-sulfinate is a good leaving group under mild condition.[10] The reaction of 2-vinyl aziridines with NBHS in the presence of triethylamine in CH_2Cl_2 provided only C-C double bond reduction products without

influencing other functional group in the side chain. The reaction was quite successful with all 1-α-methylbenzyl-(2S)-(2-alkylvinyl)aziridines including *n*-hexyl, and tridecanyl in 99, and 78% yields. 2-Aryl substituted vinylaziridines with phenyl, *p*-tolyl, 4-chlorophenyl, 4-nitrophenyl, 2-iodophenyl and 4-biphenyl at the aryl position yielded the expected double bond reduction products in more than 70% up to 95% yield. This protocol was applicable to the isomeric substrates 1-α-methylbenzyl-(2R)-(2-alkylvinyl)aziridines with *n*-propyl and phenyl substituent in 82 and 83% yield respectively. This method was highlightened by the selective double bond reduction of aziridine-2-acrylate in quantitative yield. The similar aziridine-2-acrylonitrile was reduced to 2-cyanoethylaziridine in 78% yield. The selective reduction product (**2k**) was hydrogenated in the presence of $Pd(OH)_2$ to yield 5(R)-methylpyrrolidin-2-one (**3**)[11] from the selective reduction of C(3)-N bond of the aziridine ring, debenzylation, and subsequent intramolecular cyclization in 91% yield.



Scheme 3

In this note an efficient C-C double bond reduction method of enantiomerically pure 2-vinyl substituted aziridines was described with NBHS in the presence of triethylamine in CH_2Cl_2 without breakage of aziridine ring bearing diverse functional groups in the side chain. The product 2-alkylaziridines which contain various functional group in the side chain can be the precursor of enantiomerically pure functionalized β-amino alcohols, 1,2-diamines, and nitrogen containing heterocycles.

Experimental

General. All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Air sensitive reagents and solutions were transferred *via* syringe and were introduced to the apparatus through rubber septa. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm E. Merck precoated silica gel plates (60 F254). Visualization was accomplished with either UV light, or by immersion in solutions of ninhydrine, *p*-anisaldehyde, or phosphomolybdic acid (PMA) followed by heating on a hot plate for about 10 sec. Purification of reaction products was carried out by flash chromatography using Kieselgel 60 Art 9385 (230 - 400 mesh). ^{1}H-NMR and ^{13}C-NMR spectra were obtained using a Varian Gemini-300 (300 MHz for ^{1}H, and 75 MHz for ^{13}C), or a Varian Inova-500 (500 MHz for ^{1}H, and 125 MHz for ^{13}C) spectrometer. Chemical shifts are reported relative to chloroform (δ = 7.26) for ^{1}H NMR and chloroform (δ = 77.2) for ^{13}C NMR. Data are reported as (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.) Coupling constants are given in Hz. Ambiguous assignments were resolved on the basis of standard one dimensional proton decoupling experiments. Optical rotations were obtained using a Rudolph Autopol III digital polarimeter and optical rotation data was reported as follows: $[\alpha]_D^{25}$ (concentration c = g/100 mL, solvent). Elemental analyses were performed by the Organic Chemistry Research Center at Sogang University using a Carlo Erba EA 1180 elemental analyzer. High resolution mass spectra were recorded on a 4.7 Tesla IonSpec ESI-FTMS or a Micromass LCT ESI-TOF mass spectrometer. All commercially available compounds were used as received unless stated otherwise.

General procedure for the double bond saturation reactions of 2-vinylaziridines. To a solution of 2-vinylaziridine (1 equiv) in dry CH_2Cl_2 (0.3 M) were added NBSH (4 equiv) and triethylamine (8 equiv) at 0 °C. The reaction mixture was stirred from 0 °C to RT for 12 h. The mixture became homogenous after 4 h, and the reaction mixture was stirred for another 8 h. The reaction was quenched with aqueous sat'd sodium bicarbonate (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo* to yield crude 2-alkylaiziridine as an yellow oil. Flash chromatography (SiO_2, EtOAc/hexanes, 3:7) provided products.

(R)-2-Pentyl-1-[(R)-1-phenylethyl]aziridin (2a): $[\alpha]_D^{26}$ +29.5 (c 0.35, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.25 (m, 5H), 2.38 (q, *J* = 6.6 Hz, 1H), 1.67 (d, *J* = 2.7 Hz, 1H), 1.43 (d, *J* = 6.6 Hz, 3H), 1.4-1.35 (m, 3H), 1.30-1.25 (m, 3H), 1.11-1.07 (m, 4H), 0.76 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 128.4, 127.5, 127.0, 70.1, 40.9, 33.6, 33.5, 32.0, 27.7, 23.5, 22.9, 14.3; HRMS: *m/z* calcd for $C_{15}H_{23}N$ $[M+Na]^+$ 240.1728, found 240.1728.

(R)-2-Octyl-1-[(R)-1-phenylethyl]aziridine (2b): $[\alpha]_D^{21}$ +27.4 (c 0.8, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.23 (m, 5H), 2.37 (q, *J* = 6.6 Hz, 1H), 1.67 (d, *J* = 3.0 Hz, 1H), 1.43 (d, *J* = 6.6 Hz, 3H), 1.39-1.37 (m, 2H), 1.30-1.23 (m, 4H), 1.19-1.10 (m, 5H), 1.1-1.07 (m, 5H), 0.86 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0, 128.4, 127.1, 127.1, 70.5, 39.1, 34.4, 33.1, 32.0, 29.7, 23.5, 29.4, 29.3, 27.6, 27.4, 23.0, 22.8, 14.3; HRMS: *m/z* calcd for $C_{15}H_{23}N$ $[M+Na]^+$ 282.2198, found 282.2195.

(R)-1-[(R)-1-Phenylethyl]-2-tetradecylaziridine (2c): $[\alpha]_D^{26}$ +44.3 (c 1.0, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.23 (m, 5H), 2.38 (q, *J* = 6.5 Hz, 1H), 1.68 (d, *J* = 0.3 Hz, 1H), 1.45 (d, *J* = 6.5 Hz, 3H), 1.41-1.30 (m, 2H), 1.31-1.17 (m, 19H), 1.16-1.0 (m, 8H), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0, 128.3, 127.1, 127.1, 70.5, 39.1, 34.4, 33.1, 32.1, 29.9, 29.8, 29.8, 29.8, 29.8, 29.7, 29.6, 29.6, 29.5, 29.3, 27.4, 22.9, 22.8, 14.3; HRMS: *m/z* calcd for $C_{24}H_{41}N$ $[M+H]^+$ 343.3239, found 344.3319.

(R)-2-Phenethyl-1-[(R)-1-phenylethyl]aziridine (2d): $[\alpha]_D^{26}$ +104.8 (c 0.8, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (m, 9H), 6.89 (d, *J* = 6.9 Hz, 1H), 2.50-2.24 (m, 3H), 1.67-1.63 (m, 2H), 1.58-1.55 (m, 1H), 1.43 (d, *J* = 6.6 Hz, 3H), 1.42-1.39 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 142.1, 128.5, 128.3, 127.3, 127.2, 125.7, 70.5, 38.6, 35.1, 34.2, 33.8, 23.2; HRMS: *m/z* calcd for $C_{18}H_{21}N$ $[M+Na]^+$ 274.1572, found 274.1570.

(R)-2-(4-Methylphenethyl)-1-[(R)-1-phenylethyl]aziridine

(2e): $[\alpha]_D^{21}$ +14.4 (c 0.2, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.22 (m, 5H), 7.15-7.08 (m, 4H), 2.91-2.81 (m, 1H), 2.78-2.68 (m, 1H), 2.40 (q, *J* = 6.3 Hz, 1H), 2.32 (s, 3H), 1.82-1.71 (m, 2H), 1.52-1.44 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 139.0, 135.1, 129.0, 128.5, 128.4, 127.3, 127.2, 70.5, 38.7, 35.2, 34.2, 33.3, 23.2, 21.1; HRMS: *m/z* calcd for $C_{19}H_{23}N$ $[M+Na]^+$ 288.1728, found 288.1727.

(R)-2-(4-Chlorophenethyl)-1-[(R)-1-phenylethyl]aziridine (2f): $[\alpha]_D^{26}$ +34.5 (c 0.6, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.25 (m, 5H), 7.13-7.11 (m, 2H), 6.77-6.74 (m, 2H), 2.47-2.33 (m, 1H), 2.30-2.20 (m, 1H), 1.72-1.62 (m, 2H), 1.55-1.34 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 140.4, 131.4, 129.9, 128.6, 128.4, 127.4, 127.2, 70.6, 38.3, 34.9, 34.3, 33.1, 23.2; HRMS: *m/z* calcd for $C_{18}H_{20}ClN$ $[M+Na]^+$ 308.1182, found 308.1183.

(R)-2-(4-Nitrophenethyl)-1-[(R)-1-phenylethyl]aziridine (2g): $[\alpha]_D^{21}$ +46.3 (c 0.4, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.4 Hz, 2H), 7.39-7.26 (m, 5H), 6.92 (d, *J* = 8.4 Hz, 2H), 2.59-2.49 (m, 1H), 2.42-2.33 (m, 2H), 1.83-1.71 (m, 2H), 1.55-1.26 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 144.9, 139.9, 129.2, 128.6, 127.4, 127.2, 123.5, 70.6, 37.9, 34.3, 33.6, 29.8, 23.0; HRMS: *m/z* calcd for $C_{18}H_{20}N_2O_2$ $[M+Na]^+$ 319.1422, found 319.1423.

(R)-2-(2-Iodophenethyl)-1-[(R)-1-phenylethyl]aziridine (2h): $[\alpha]_D^{21}$ +59.7 (c 1.65, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.5 Hz, 1H), 7.43-7.23 (m, 5H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.80 (t, *J* = 8.4 Hz, 2H), 2.58-2.48 (m, 2H), 2.45-2.38 (m, 2H), 1.78-1.67 (m, 3H), 1.58-1.50 (m, 1H), 1.44 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 144.5, 139.5, 129.5, 128.5, 128.3, 127.7, 127.3, 127.1, 100.5, 70.5, 38.8, 38.6, 34.1, 33.6, 23.2; HRMS: *m/z* calcd for $C_{18}H_{20}IN$ $[M+Na]^+$ 400.0538, found 400.0536.

(R)-2-(4-Bromo-2-fluorophenethyl)-1-[(R)-1-phenylethyl] aziridine (2i): $[\alpha]_D^{19}$ +18.5 (c 0.3, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.26 (m, 5H), 7.11-7.03 (m, 2H), 6.54 (t, *J* = 7.8 Hz, 1H), 2.49-2.22 (m, 4H), 1.70-1.62 (m, 2H), 1.48-1.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 160.0, 145.1, 131.9, 131.9, 128.6, 127.9, 127.4, 127.2, 127.1, 127.1, 119.6, 119.5, 119.0, 118.8, 70.5, 38.4, 34.2, 33.3, 26.9, 23.2; HRMS: *m/z* calcd for $C_{24}H_{25}N$ $[M+Na]^+$ 370.0583, found 370.0586.

3-{(R)-1-[(R)-1-Phenylethyl]aziridin-2-yl} propanenitrile (2j): $[\alpha]_D^{21}$ +138.5 (c 1.0, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5H), 2.44 (q, *J* = 6.3 Hz, 1H), 2.08-1.98 (m, 1H), 1.84-1.76 (m, 3H), 1.53-1.31 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 128.6, 127.5, 127.0, 119.4, 70.1, 37.0, 34.2, 28.9, 22.2, 15.0; HRMS: *m/z* calcd for $C_{13}H_{16}N_2$ $[M+Na]^+$ 223.1211, found 223.1213.

3-{(R)-1-[(R)-1-Phenylethyl]aziridin-2-yl)} propanenitrile (2k): $[\alpha]_D^{21}$ +138.5 (c 1.0, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5H), 2.44 (q, *J* = 6.3 Hz, 1H), 2.08-1.98 (m, 1H), 1.84-1.76 (m, 3H), 1.53-1.31 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 128.6, 127.5, 127.0, 119.4, 70.1, 37.0, 34.2, 28.9, 22.2, 15.0; HRMS: *m/z* calcd for $C_{13}H_{16}N_2$ [M+Na] + 223.1211, found 223.1213.

(S)-2-Pentyl-1-[(R)-1-phenylethyl]aziridine (2a'): $[\alpha]_D^{21}$ + 64.4 (c 0.6, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.23 (m, 5H), 2.39 (q, *J* = 6.4 Hz, 1H), 1.56-1.24 (m, 14H), 0.92-0.90 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 128.5, 128.4, 127.0, 70.1, 40.9, 33.6, 33.5, 31.9, 27.7, 23.5, 22.9, 14.3; HRMS: *m/z* calcd for $C_{15}H_{23}N$ $[M+Na]^+$ 240.1728, found 240.1728.

(S)-2-Phenethyl-1-[(R)-1-phenylethyl]aziridine (2b'): $[\alpha]_D^{26}$ +24.4 (c 0.25, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.18 (m, 10H), 2.95-2.72 (m, 2H), 2.40 (q, *J* = 6.4 Hz, 1H) 1.89-1.69 (m, 2H), 1.52-1.44 (m, 5H), 1.27 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 142.1, 128.6, 128.5, 128.5, 127.1, 127.0, 126.0, 70.0, 40.3, 35.0, 34.2, 33.6, 23.5; HRMS: *m/z* calcd for $C_{18}H_{21}N$ $[M+Na]^+$ 274.1572, found 274.1574.

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7. Unpublished results. Catalytic hydrogenation of 2-vinyl substituted aziridines provides a mixture of ring C-N bond reduction product and also side chain reduction product. The C(2)-N bond energy difference calculation, between N-methyl-2-ethylaziridine and N-methyl-2-vinylaziridine, was performed on a PC using Spartan'04 Quantum Mechanics Program (PC/X86). The optimization of the geometry of neutral molecules and radicals were preliminarily obtained by a PM3 semiempirical method. The energy minimizations were then performed using B3LYP functional. The 6-31+G*, 6-31G* and 6-311+G* were used for all C, H, O, N, S, Cl atoms. All geometry optimizations were performed without symmetry constraints to ensure that the resultant geometry is not a local minimum. The absolute energies of the calculated species were obtained without corrections for zero point vibrational energy. The homolytic bond dissociation energy (E^{homol}(BD)) for all species investigated was calculated using the equation: (E^{homol}(BD)) = [E^{abs}(radical^1) = E^{abs}(radical^2)] - E^{abs}(neutral molecule).

The calculation shows the C(2)-N bond energy of N-methyl-2-vinylaziridine is 14.9 kcal/mol less than that of the N-methyl-2-ethylaziridine.

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