A short and efficient Formal Synthesis of R-Pipecolic Acid from the Ring expansion of Chiral Aziridine

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Research Article

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Abstract

Ring expansion of 4-(*R*)-1-(*R*)-1-phenylethyl)aziridin-2-yl)butyl 4-tosylate obtained from tosylation of 4-(*R*)-1-(*R*)-1-phenylethyl)aziridin-2-yl)butan-1-ol via formation of 1-azabicyclo[4.1.0]heptane tosylate gives substituted piperidine. The ring openings of azabicycloheptane tosylate with acetate nucleophiles proceeded in highly regio- and stereoselective manner with release of the ring-strain of the three-member aziridine ring through the breakage of either C-N bond. This ring expansion streategy of aziridine provides a short route for asymmetric synthesis of biologically active natural alkaloid such as *R*-Pipecolic acid.

Introduction

Aziridine, a three-membered heterocyclic compound with nitrogen as a hetero atom, has similar ring strain as other three-membered cyclic organic compounds such as cyclopropane and oxirane. These cyclic strained organic molecules has many synthetic utility due to their ring openining reactions in highly regio- and stereoselective manner [1–9]. In comparision to cyclopropane and oxirane, ring opening of aziridines were less explored because of its less reactivity and selectivity [10–12]. However, openining of aziridine ring depends on the substituents present on nitrogen. Based on the nature of substituents present on nitrogen, there are two types of aziridine, first one is aziridine with electron donating group called non-activated aziridine and second one with electron withdrawing substituents at nitrogen called activated aziridines (Fig. 1).

Activated aziridines are quite reactive towards ring opening reaction without further activation [13, 14], while non-activated aziridine is quite stable and inert to the nucleophiles, unless it is activated as an aziridinium ion (Scheme 1) [15–21]. Activation of aziridine nitrogen with external electrophile (**3a**) followed by ring opening reaction results in the formation of acyclic compound **4**. In-situ formation and characterization of an bicyclic aziridinium ion were observed spectroscopically with non-reactive counting anion [18, 19, 21]. Proper selection of activating agents i.e. electrophylic reagent and the nucleophile may afford pyrrolidine (**6**) and piperidines (**7**) via the regio- and stereoselective ring-opening reaction [15–21].

Piperidines are the key structural features present in several biologically active natural products especially alkaloids such as fagomine (**8**) an glycosidase inhibitors [22, 23], febrifugine (**9**) [24, 25], tetrazomine (**10**) [26], sedamine (**11**) [27], swainsonine (**12**) [11], pipecolic acid (**13**) [11], isosolenopsin (**14**) [20, 28–31], deoxocassine (**15**) [20, 32–35] and spectaline (**16**) [36, 37].

(*S*)-Pipecolic acid (**13**), is a cyclic amino acid and present in the structure of several biologically active alkaloid such as immunosuppressors rapamycin [38, 39], FK506, immunomycin [40], and ropivacaine [41]. The unique structural features and inherent biological activity of pipecolic acid have attracted many chemists to attempt its synthesis. There are a few literature reports of synthesis of pipecolic acid from resolution of racemic compound and from application of carbohydrate chemistry using multiple steps. Herein, we report a short and efficient formal synthesis of *R*-pipecolic acid using chiral aziridine.

Results and Discussion

In continuation of our interest in the preparation of bicyclic aziridinium ion and its subsequent ring opening reactions with various nucleophiles to generate piperidine ring system, we attempt the formal synthesis of pipecolic acid from chiral aziridine [15–20]. Accordingly, compound **14** was treated with freshly recrystallized *p*-toluenesulphonyl chloride in presence of triethylamine and DMAP base in CH_2Cl_2 to afford the tosylate compound **15** in 94% yields. The tosylate compound **15** after purification by flash column chromatography was found to be unstable in CH_2Cl_2 and complete decomposition was observed in 6 hrs as confirmed by TLC. However compound **15** when dissolved in anhydrous acetonitrile under N_2 atmosphere and kept for 24 hrs at room temperature, it converted to bicyclic aziridinium ion **16** [19]. Structure of compound **16** was confirmed by NMR spectrum. Compound **16** was further reacted with sodium acetate in acetonitrile at 0°C to room temperature for 12 hrs to give aziridine ring expanded product **17** along with minor product **17a** in 96% combined yield in the ratio of 4:1 favoring desired piperidine compound **17**. Acetate deprotection of piperidine **17** with sodium methoxide in methanol followed by debenzylation in presence of $(Boc)_2O$ afforded compound **18** in 77% yields. Deprotection of Boc group followed by oxidation of hydroxymethyl group of compound **18** using reported procedure will give *R*-pipecolic acid (**13**) [11]. All the products were characterized by NMR spectroscopy and Mass spectrometry and the analytical data are in good agreement with those reported in literature (Scheme 2) [11].

Conclusions

In conclusion, the short and efficient formal synthesis of (*R*)-pipecolic acid has been achieved from ring expansion reaction of 1-azabicyclo[4.1.0]heptane tosylate. This synthetic route enable us to synthesise various piperidine containing alkaloid in very short and efficient route with excellant chiral purity.

Experimental Section

Materials and methods

Chiral aziridines are available from Aldrich. All commercially available compounds were used as received unless stated otherwise. All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirrer. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm E. Merck pre-coated silica gel plates (60 F254). Visualization was accomplished with either UV light, or by immersion in solutions of ninhydrin, *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 (100–200 mesh). ^{1}H-NMR and ^{13}C-NMR spectra were obtained using Bruker AVANCE 400 MHz spectrometer. Chemical shifts are reported relative to acetonitrile (δ = 1.94), chloroform (δ = 7.26) for ^{1}H NMR and acetonitrile (δ = 118.26), chloroform (δ = 77.0) for ^{13}C NMR. Data are reported as (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, m =

multiplet). Coupling constants are given in Hz. Optical rotations were obtained JASCO P-2000.Optical rotation data was reported as follows: $[\alpha]^{20}$ (concentration c = g/100 mL, solvent).

4-[(R)-1-(R)-1-Phenylethyl)aziridin-2-yl]butyl-4-methylbenzenesulfonate (15): To a stirred solution of aziridinyl alcohol **14** [20] (600 mg, 2.74 mmol) and Et_3N (1.15 mL, 8.22 mmol) in 100 mL two neck round bottom flask in anhydrous CH_2Cl_2 (15 mL) at 0°C was added *p*-toluenesulfonyl chloride (781 mg, 4.11 mmol) freshly recrystallized from hexanes followed by catalytic DMAP (33 mg, 0.27 mmol) under N_2 atmosphere. The resulting mixture was stirred for another 2 hrs at rt and the completion of reaction was confirmed by TLC (EtOAc: hexanes, 7:3). After complete conversion of starting alcohol, the reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 x 30 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuums to get crude tosylate, which was purified by flash column chromatography to get pure tosylate **15** (961 mg, 94% yield) as a viscous liquid. ^{1}H NMR (400 MHz, CD_3CN) δ = 7.73 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.35–7.13 (m, 5H), 3.76 (t, J = 6.4 Hz, 2H), 2.45 (s, 3H), 2.37 (q, J = 6.5 Hz, 1H), 1.50 (d, J = 3.2 Hz, 1H), 1.39–1.17 (m, 8H), 1.11–0.91 (m, 3H). ^{13}C NMR (101 MHz, CD_3CN) δ = 146.4, 146.2, 133.9, 130.9, 129.0, 128.6, 127.9, 127.8, 71.8, 70.5, 38.9, 34.0, 32.6, 28.7, 23.7, 23.0, 21.6 ppm.

(6*R*)-1-(*R*)-1-phenylethyl)-1-azoniabicyclo[4.1.0]heptane tosylate (16)

The freshly prepared 4-[(*R*)-1-(*R*)-1-Phenylethyl)aziridin-2-yl]butyl-4-methylbenzenesulfonate (**15**) (900 mg, 2.41 mmol) was stored in anhydrous CH_3CN (20 mL) at room temperature for 24h to accomplish the complete conversion to bicyclic aziridinium ion **16** as confirmed by NMR spectrum. ^{1}H NMR (400 MHz, CD_3CN) δ = 7.65–7.49 (m, 7H), 7.15 (d, J = 7.8 Hz, 2H), 4.12 (q, J = 7.0 Hz, 1H), 3.82–3.74 (m, 1H), 3.48 (dt, J = 13.3, 5.3 Hz, 1H), 3.24 (dd, J = 9.0, 4.2 Hz, 1H), 3.19–3.11 (m, 1H), 3.04 (dd, J = 7.9, 4.2 Hz, 1H), 2.33 (s, 3H), 2.15–2.02 (m, 2H), 1.72 (d, J = 7.0 Hz, 3H), 1.53–1.43 (m, 1H), 1.38–1.28 (m, 2H), 0.94–0.82 (m, 1H). ^{13}C NMR (101 MHz, CD_3CN) δ = 146.7, 139.4, 134.5, 131.2, 130.2, 129.4, 129.2, 126.6, 71.9, 49.7, 49.5, 43.0, 21.2, 20.7, 15.5, 14.0 ppm.

[(R)-1-(R)-1-Phenylethyl)piperidin-2-yl)]methyl acetate (17): To a stirred solution of (6*R*)-1-(*R*)-1-phenylethyl)-1-azoniabicyclo[4.1.0]heptane tosylate (**16**) (900 mg, 2.41 mmol) in 25 mL anhydrous acetonitrile at 0°C was added anhydrous sodium acetate (592 mg, 7.23 mmol) and reaction mixture was allowed to stir for 12 hrs at room temperature. After completion of reaction as confirmed from TLC, the reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layer were dried over Na_2SO_4 and concentrated under vacuum to get crude product, which was purified by column chromatography using 10% EtOAc: hexanes to get 483 mg of compound **17** and 120 mg of compound **17a** in 96% combined yield. Analytical data of compound **17**: $[\alpha]^{20}_D$ = + 74.5 (c = 0.43, $CHCl_3$). ^{1}H NMR (400 MHz, CD_3CN) δ = 7.37–7.14 (m, 5H), 4.27 (dd, J = 11.3, 4.8 Hz, 1H), 4.18–4.08 (m, 1H), 4.02 (q, J = 6.8 Hz, 1H), 2.78–2.66 (m, 2H), 2.37 (ddd, J = 12.1, 6.2, 3.4 Hz, 1H), 1.94 (s, 3H), 1.65–1.40 (m, 5H), 1.38–1.18 (m, 4H). ^{13}C NMR (101 MHz, CD_3CN) δ = 171.5, 145.1, 128.9, 128.5, 127.5, 63.7, 59.3, 55.6,

45.3, 28.7, 26.2, 22.1, 21.1, 20.9 ppm. HRMS-MALDI (m/z): calcd. for $C_{16}H_{24}NO_2$ $[M + H]^+$ 262.1801; found 262.1803.

Analytical data of compound **17a**: **(S)-1-[(R)-1-Phenylethyl)]azepan-3-yl acetate (17a)**: $[\alpha]^{20}_D$ = − 57.9 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, CD_3CN) δ = 7.43–7.17 (m, 5H), 4.83–4.72 (m, 1H), 3.83 (q, *J* = 6.8 Hz, 1H), 2.89 (dd, *J* = 14.0, 4.7 Hz, 1H), 2.68–2.54 (m, 3H), 1.93–1.90 (m, 1H), 1.86 (s, 3H), 1.71–1.43 (m, 5H), 1.32 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CD_3CN) δ = 170.9, 145.4, 128.9, 128.4, 127.5, 74.9, 64.1, 56.0, 54.2, 33.4, 30.5, 22.2, 21.4, 17.5 ppm. HRMS-MALDI (m/z): calcd. for $C_{16}H_{24}NO_2$ $[M + H]^+$ 262.1801; found 262.1809.

(2 S,3R)-tert-Butyl-3-hydroxy-2-(hydroxymethyl)piperidine-1-carboxylate (18): To the stirred solution of [(*R*)-1-(*R*)-1-Phenylethyl)piperidin-2-yl)]methyl acetate **17** (400 mg, 1.53 mmol) in methanol (15 mL) was added CH_3ONa (82 mg, 1.16 mmol) and the reaction mixture was stirred for 1 hr at room temperature. After complete conversion of starting acetate as confirmed by TLC (25% EtOAc/Hexane), methanol was removed under vacumm and the crude product was dissolved in water and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to get crude alcohol, which was used as such for next reaction. The crude alcohol obtained was dissolved in methanol (15 mL) and degas for 30 minutes. $(Boc)_2O$ (833 mg, 3.82 mmol), triethylamine (0.53 mL, 3.82 mmol) and $Pd(OH)_2/C$ (40 mg, 50% wet) was added and reaction was stirred under H_2 balloon for 12 hrs. After complete conversion, reaction mixture was filtered using celite and washed with methanol. The combined organic layer were concentrated under vaccum and crude product was purified by column chromatography to get pure compound **18** (312 mg, 95% yield) as a white solid. R_f: 0.7 (50% EtOAc/Hexane), m.p. 82–84°C. $[\alpha]^{20}_D$ = + 37.8 (*c* = 0.85, $CHCl_3$). [lit. [11] reported for enantiomer, $[\alpha]^{25}_D$ − 40.5 (*c* 1.0, $CHCl_3$]. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.34–4.22 (m, 1H), 3.93 (d, *J* = 12.9 Hz, 1H), 3.80 (td, *J* = 10.8, 4.9 Hz, 1H), 3.65–3.53 (m, 1H), 2.85 (t, *J* = 11.6 Hz, 1H), 2.30 (br s, 1H), 1.75–1.36 (m, 15H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.3, 79.8, 61.4, 52.4, 40.0, 28.5, 25.3, 25.2, 19.5 ppm. HRMS-MALDI (m/z): calcd. for $C_{12}H_{21}NO_3Na$ $[M + Na]^+$ 238.1413; found 238.1416.

Declarations

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Schemes

Schemes 1 and 2 are available in the Supplementary Files section.

Figures

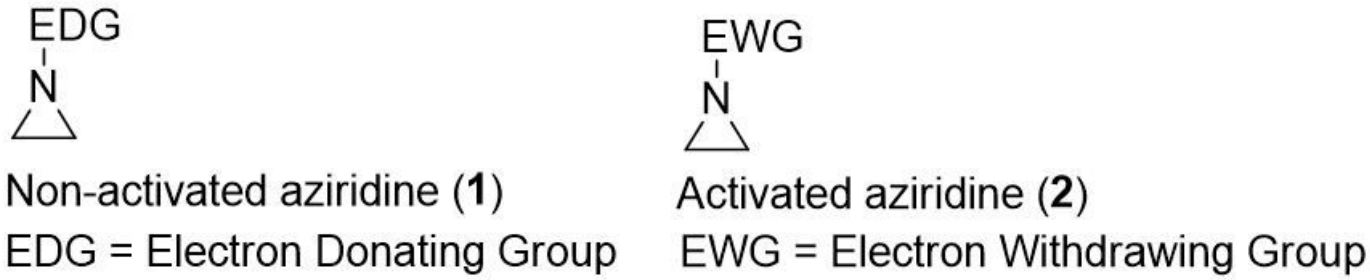

Figure 1

Structure of Non-activated and Activated aziridines

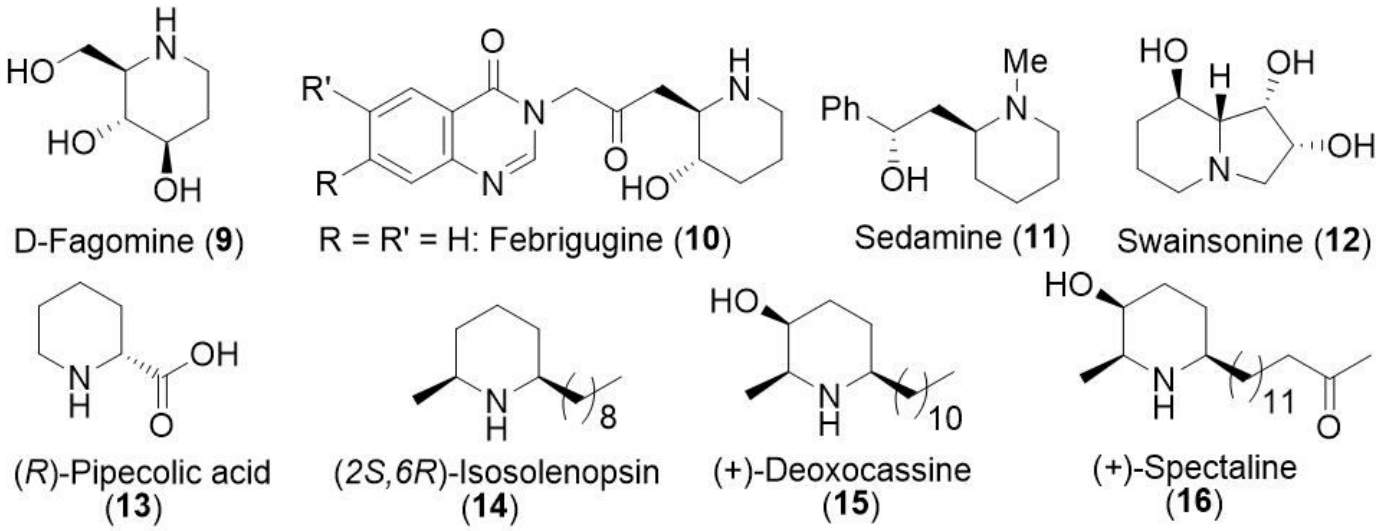

Figure 2

Structures of few biologically active piperidines

Supplementary Files

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