Regioselective Bromination of 6-Hydroxytetrahydroisoquinolines

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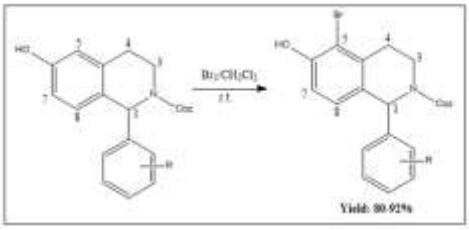

Regioselective bromination of 6-hydroxytetrahydroisoquinolines using molecular bromine was disclosed. Treatment of 6-hydroxytetrahydroisoquinolines with molecular bromine under different temperatures afforded 5-bromo-6-hydroxytetrahydroisoquinolines as sole products in high isolated yield with excellent regioselectivity.

Key words: Regioselectivity, bromination, tetrahydroisoquinoline

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INTRODUCTION

1,2,3,4-tetrahydroisoquinolines are important compounds of great interest due to their significantly biological and pharmacological activities. They are common structural moieties in biologically active compounds and important intermediates in organic synthesis. For instance, 1-methyl- and 1-phenyl-tetrahydroisoquinolines are involved in the treatment of Parkinson's and other nervous diseases[1]. Moreover, tetrahydroisoquinoline derivatives display a wide range of biological activities, such as anti-HIV, antitumor, antipsychotic, antidiabetes, ß-adrenoceptor antagonist and so on[2]. In addition, tetrahydroisoquinolines are also key intermediates for the synthesis of more complex natural alkaloids, represented by saframycins, renieramycins, lemonomycins and ecteinascidins[3], which possess potential antitumor and antimicrobial activities.

The bromination of aromatics is a common transformation in organic chemistry. These brominated compounds not only exhibit a wide variety of biological activities, but also can be used for the carbon-carbon bond formation via cross-coupling reaction such as Suzuki[4], Heck[5], and Sonogashira[6], or the carbon-heteroatom bond formation.

So far, no synthetic study has been reported on the bromination of tetrahydroisoquinolines. In the present paper, we reported an efficiently regioselective bromination of 6-hydroxytetrahydroisoquinoline derivatives using molecular bromine in CH_2Cl_2 solution, which would provide invaluable synthetic intermediates for the synthesis of complex natural products and active pharmaceuticals.

RESULTS AND DISCUSSIONS

The synthetic route is outlined in Scheme 1. In the presence of acetic acid, the reaction of

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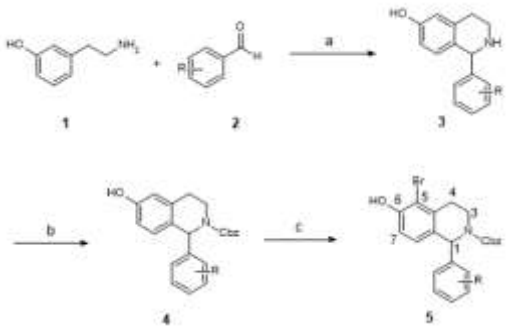
3-hydroxyphenethylamine **1** with benzaldehyde **2** in methanol solution proceeded smoothly to give 6-hydroxytetrahydroisoquinoline **3** via Pictect-Spengler reaction, followed by *N*-protected with CbzCl. Treatment **4** with one equivalent of bromine in CH_2Cl_2 solution afforded corresponding brominated product.



Scheme1. Reagents and conditions: (a) CH_3COOH, CH_3OH, 50°C; (b) CbzCl, $NaHCO_3$, $CHCl_3$, H_2O; (c) Br_2, CH_2Cl_2.

At first, we chose *N*-protected tetrahydroisoquinoline **4a** bearing 1-phenyl substituent as the model molecule to investigate the regioselectivity of the bromination under different reaction temperatures. The results are summarized in Table 1.

Table 1.

As can be seen from Table 1, an excellent regioselectivity was observed. No matter at what temperature the reaction was carried out, 5-bromo-6-hydroxytetrahydroisoquinoline **5a** was produced as the sole product without detectable 7-bromo or 5,7-dibromo product. Moreover, with the increase of temperature from -78°C to 25°C, the isolated yield was dramatically increased from 59% to 92%. The product **5a** was separated by column chromatography and its structure was characterized by ^{1}H NMR, ^{13}C NMR and HRMS. According to the above results, the room temperature was ultimately chosen as the optimum reaction condition due to its operational convenience and higher yield.

To establish the scope of this bromination procedure, other eleven 6-hydroxytetrahydroisoquinoline derivatives were investigated. The reactions were carried out under room temperature and the results are presented in Table 2. It was clear that this method was both general and efficient. In all cases, 6-hydroxytetrahydroisoquinolines resulted in conversion to the desired 5-bromo-6-hydroxytetrahydroisoquinolines in over 80% isolated yield with excellent regioselectivity.

Table 2.

Thus a remarkably regioselective bromination technique was discovered for 6-hydroxytetrahydroisoquinolines, which specifically afforded corresponding 5-bromo products in over 80% isolated yield. The reason leading to this result was apparently owing to the specific structure of the 6-hydroxytetrahydroisoquinoline molecules. When 6-hydroxytetrahydroisoquinoline reacted with molecular bromine, the reactivity of C-5 was much higher than C-7, which was possibly due to the fact that both steric hindrance effect of the 1-aryl substituents and electronic effects were beneficial for the formation of 5-bromo-6-hydroxytetrahydroisoquinoline.

CONCLUSION

In conclusion, an efficient and facile method was established for the preparation of 5-bromo-6-hydroxytetrahydroisoquinoline derivatives through the highly regioselective bromination of 6-hydroxytetrahydroisoquinolines with molecular bromine in CH_2Cl_2 solution.

EXPERIMENTAL

General. All reagents and solvents were pure analytical grade materials purchased from

commercial sources and were used without further purification, if not stated otherwise. ^{1}H NMR (300 or 400 MHz) spectra were recorded at 24 ^{o}C. The data was reported as chemical shift (ppm), and the interpretation of peak with relevant coupling constants reported in Hertz. ^{13}C NMR spectra were recorded at 75MHz spectrometer at 24^{o}C. Mass spectra were obtained using an ion trap mass spectrometer equipped with electrospray ionization (ESI) ion source.

General procedure:

Synthesis of 6-hydroxytetrahydroisoquinoline (3a)

To a solution of 3-hydroxyphenethylamine **1** (1.00 g, 7.30 mmol), benzaldehyde **2** (0.89 mL, 8.76 mmol) and 4Å molecular sieves (1.00 g) in methanol (15 mL) was added acetic acid (1.67 mL, 29.20 mmol) dropwise. The mixture was stirred at 50 ^{o}C for 5 h under argon. After filtration, the organic solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product. Purification by column chromatography (CH_2Cl_2/CH_3OH = 50:1) afforded 6-hydroxytetrahydroisoquinoline **3a** (1.38 g, 84%) as a white solid. M.p.=108-110^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.57 (s, 1H), 7.43-7.37 (m, 5H), 6.65 (d, *J* = 2.0 Hz, 1H), 6.57 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.47 (d, *J* = 8.4 Hz, 1H), 5.50 (s, 1H), 3.33-3.22 (m, 2H), 3.15-3.12 (m, 1H), 2.94-2.90 (m, 1H); HRMS calcd for $C_{15}H_{16}NO$ $[M+H]^+$ 226.1226, found 226.1119.

Synthesis of compound 4a

To a stirred mixture of 6-hydroxytetrahydroisoquinoline **3a** (0.855 g, 3.80 mmol), $NaHCO_3$ (798 mg, 9.50 mmol), $CHCl_3$ (12 mL) and H_2O (9.0 mL), was added a solution of benzyloxy carbonyl chloride (0.61 mL, 4.26 mmol) in $CHCl_3$ (3 mL) under cooling below 5^{o}C. The mixture was stirred at 5^{o}C for 1 h and then at room temperature for 2 h. The $CHCl_3$ layer was separated, washed with H_2O, 5% aqueous HCl and H_2O, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography (PET/EtOAc = 5:1) to afford *N*-Cbz protected product **4a** (1.03 g, 76%) as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (s, 1H), 7.35-7.21 (m, 8H), 7.15 (d, *J* = 7.2 Hz, 2H), 6.94 (d, *J* = 5.6 Hz, 1H), 6.61 (s, 1H), 6.60 (d, *J* = 5.6 Hz, 1H), 6.17 (s, 1H), 5.17 (d, *J* = 12.4, 1H), 5.10 (d, *J* = 12.4 Hz, 1H), 3.85-3.83 (m, 1H), 3.30-3.26 (m, 1H), 2.83-2.75 (m, 1H), 2.70-2.66 (m, 1H); HRMS calcd for $C_{23}H_{22}NO_3$ $[M+H]^+$ 360.1594, found 360.1594.

Synthesis of compound 5a

To a solution of *N*-Cbz protected compound **4a** (0.898 g, 2.50 mmol) in CH_2Cl_2 (20 mL) was added bromine (0.13 mL, 2.50 mmol) in CH_2Cl_2 (15 mL) dropwise. The mixture was stirred for 2 h and then was washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography (PET/EtOAc = 7:1) afforded corresponding brominated product **5a** (1.01 g, 92%) as a yellow solid. M.p.=143-145^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H), 7.37-7.25 (m, 8H), 7.14 (d, *J* = 6.8 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.24 (s, 1H), 5.18 (d, *J* = 12.4 Hz, 1H), 5.12 (d, *J* = 12.4 Hz, 1H), 3.99-3.95 (m, 1H), 3.20-3.13 (m, 1H), 2.84-2.76 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.1(2C), 142.4, 136.7, 135.2(2C), 128.4(2C), 128.3(2C), 128.1, 127.9, 127.8(2C), 127.6, 127.3, 127.2, 114.1, 111.6, 66.6, 56.6, 37.4, 29.1; HRMS calcd for $C_{23}H_{21}BrNO_3$ $[M+H]^+$ 438.0699,

found 438.0685.

Supporting Information: Full experimental detail, ^{1}H NMR spectra, ^{13}C NMR spectra, HRMS.

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