Preliminary Communication

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Efficient synthesis of 6-amino-2-thiaspiro[3,3] heptane hydrochloride

Abstract: A novel compound 6-amino-2-thiaspiro[3,3]heptane hydrochloride was synthesized in nine steps using 2,2-bis(bromomethyl)-1,3-propanediol as starting material, with an overall yield of 31%.

Keywords: 6-amino-2-thiaspiro[3,3]heptane; 2,2-bis-(bromomethyl)-1,3-propanediol; synthesis.

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Introduction

Unique properties of spiro heterocyclic compounds are spiroconjugation, spirohyperconjugation, and anomeric effect. Because their special space configurations can usually match different spatial structures of macromolecules in organisms, these compounds can show significant biological activity [1]. The spiro compounds are widely used as a pharmacophore unit in the synthesis of antineoplastic [2], antidepressant [3, 4], antiviral [5], antibacterial [6], and antianxiety [7–9] drugs.

Spiro[3,3]heptane and its derivatives has recently been used as the surrogates of piperazines, piperidines, morpholines, and thiomorpholines, which display pharmacological activity [10–12]. For example, Radchenko et al. [13] have reported the synthesis of 6-amino-2-azaspiro[3,3]heptane-6-carboxylic acid and 2-azaspiro[3,3]heptane-6-carboxylic acid, which are analogues of natural ornithine and γ-aminobutyric acid. These amino acids are sterically constrained compounds and can be selective ligands for various biological targets that are especially popular in the design of peptidomimetic drugs. The sterically constrained cyclobutane diamine derivative 6-amino-3-azaspiro[3,3] heptane has been evaluated as inhibitor of kinases CDK1, CDK2, CDK5, GSK-3, and PLK and can be used as insecticides and acaricides [14]. Fang et al. [15] have reported a new class of indole spiro compounds, which can be used for the treatment and prophylaxis of respiratory syncytial virus infection. Rice and Gorgan [16] have reported that the bismethonium salt derivatives of spiro[3,3]heptane have a weak hypotensive and curarimimetic activity. Therefore, design and synthesis of new spiro[3,3]heptane compounds, especially the spiro heterocyclic compounds, with better biocompatibility are of great significance for the development and efficacy of new drug screening.

In this paper, the short and efficient synthesis of a novel compound 6-amino-2-thia-spiro[3,3]heptane hydrochloride (**10** in Scheme 1) is reported. The cheap compound 2,2-bis(bromomethyl)-1,3-propanediol (**1**) was used as the starting material. To protect the two exposed hydroxyls in **1**, as originally proposed by Allinger and Tushaus [17], its dioxane dibromo derivative **2** was used in the synthesis. The treatment of dibromide **2** with malonic ester under basic conditions gave a diester derivative **3** with a cyclobutane structure. Similar syntheses have been reported [18]. This diester was hydrolyzed to the dicarboxylic acid **4**. After a subsequent decarboxylation process [19], the monocarboxylic acid **5** was obtained. The resultant monocarboxylic acid derivative **5** was efficiently converted into *N*-Boc-protected amino derivative **6** by treatment with diphenylphosphoryl azide (DPPA) and triethylamine (Et_3N) in *tert*-butanol (*t*-BuOH). There are two ways of converting carboxylic acid to amine reported in the literature. In the first method, carboxylic acid is allowed to react with thionyl chloride or ethyl chloroformate to give an acyl chloride or ester, the treatment of which with ammonium hydroxide produces an amide. The amide can then be

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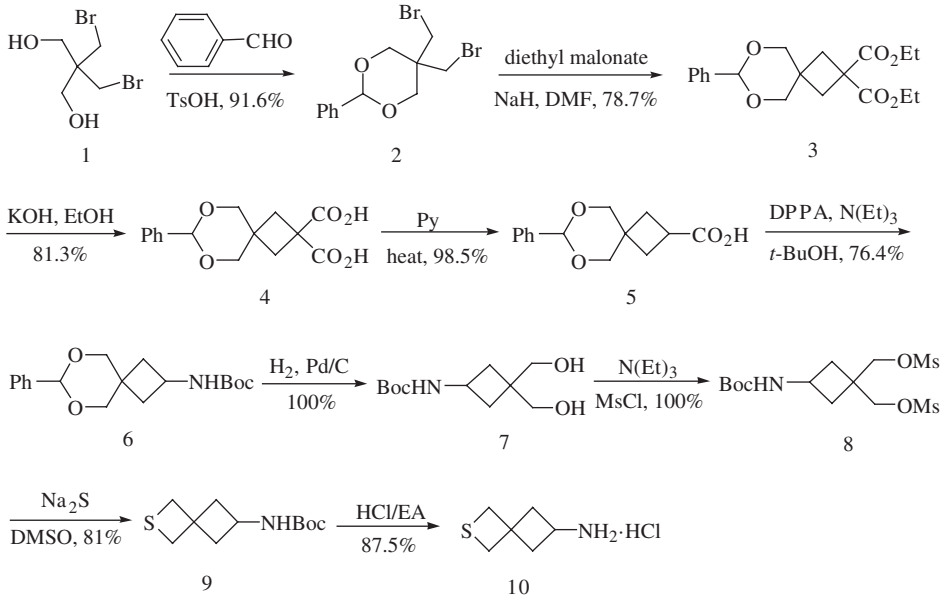

Scheme 1 Total synthesis of 6-amino-2-thiaspiro[3,3]heptane hydrochloride (**10**).

converted into an amino derivative [20, 21]. This method is complex and the yield is low. The superior second method [22–24] is shown in Scheme 1. Then, the protected diol moiety in **6** is deprotected by reduction with hydrogen to give the diol 7. This reaction was followed by mesylation, which yielded the bis-methanesulfonate ester **8**, the bis-sulfonate functionality of which was transformed into a thiaspiro derivative **9** by reaction with sodium sulfide. In principle, the introduction of the sulfur atom in **9** could be accomplished starting with the bis-halomethyl analogues of **8**. Such preparations are common in the literature [25–28]. However, compound **7** proved to be difficult to convert to a halide derivative. By contrast, the sulfonylation of 7 was efficient, and the resultant bis-ester **8** was easily cyclized into the thia derivative **9**. As can be seen in Scheme 1, the desired product **10** was obtained by acid hydrolysis of the Boc-protected 2-thiaspiro[3,3]heptane **9**.

In summary, 6-amino-2-thia-spiro[3,3]heptane (**10**) was successfully prepared in nine steps from commercially available starting materials, with an overall yield of 31%. The efficient synthetic procedures were designed based on a critical evaluation of analogous literature preparations.

Experimental details

Reactions were monitored by thin-layer chromatography (TLC) using Sanpont Silica gel GF254 plates. In addition, preparative chromatography (flash chromatography) was performed on silica gel (200–300 mesh) column, eluting with pentane/ethyl acetate (9:1). Melting points were measured on a WRS-2A apparatus. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AVANCE 400 spectrometer at room temperature. FT-IR spectra were obtained in KBr pellets on Avatar360 spectrometer. Mass spectra were acquired using a Waters Acquity-Quaptro Premier spectrometer equipped with electrospray ionization (ESI) source or chemical ionization (CI) source.

5,5-Bis(bromomethyl)-2-phenyl-1,3-dioxane (2)

To a four-neck flask equipped with a thermometer, water segregator, and condenser, 1,3-dibromo-2,2-dihydroxymethylpropane (**1**, 164.9 g, 0.63 mol), benzene (250 mL), benzaldehyde (73.5 g, 0.69 mol), and *p*-toluenesulfonic acid (1.1 g, 5.78 mmol) were added. The mixture was heated under reflux until water removal was completed, then cooled to ambient temperature, washed with aqueous sodium carbonate, dried with anhydrous potassium carbonate, and concentrated under reduced pressure, and the residue was crystallized from methanol at -10°C to give product **2** (202 g, 92%) as a white solid; mp 70.8–71.0°C; IR: 3095, 3030, 3017, 2863, 2834, 2749, 2714, 1960, 1495, 1450, 1259, 1121, 1029, 832, 743, 694, 683, 667, 643 cm^{-1}; CI-MS: *m/z* 350.85 [(M+H)$^+$]; ^{1}H NMR ($CDCl_3$): δ 7.48–7.24 (5H, m), 5.39 (1H, s), 4.24 (2H, d, *J* = 12 Hz), 3.97 (2H, s), 3.84 (2H, d, *J* = 12 Hz), 3.30 (2H, s); ^{13}C NMR ($CDCl_3$): δ 137.5, 129.5, 128.6, 126.3, 102.5, 72.2, 37.6, 36.3, 34.7. Anal. Calcd for $C_{12}H_{14}Br_2O_2$: C, 41.17; H, 4.03; Br, 45.65. Found: C, 41.19; H, 4.00; Br, 45.64.

7-Phenyl-6,8-dioxa-spiro[3,5]nonane-2,2-dicarboxylic acid diethyl ester (3)

Diethyl malonate (22.3 g, 0.14 mol) was added dropwise to a suspension of sodium hydride (5.4 g, 60%) in DMF (230 mL). Then,

5,5-bis-(bromomethyl)-2-phenyl-1,3-dioxane (**2**, 24.0 g, 0.07 mol) was added, and the mixture was heated at 140°C for 4 h under N_2 atmosphere, cooled, and extracted with aqueous ammonium chloride and methyl *tert*-butyl ether. The organic layer was concentrated, and the residue was crystallized from petroleum ether to give 18.8 g (79%) of compound **3**; mp 82.5–83.3°C; IR: 3092, 3037, 2855, 1962, 1724, 1498, 1478, 1458, 1274, 1172, 1098, 761, 702 cm^{-1}; CI-MS: *m/z* 349.10 $[(M+H)^+]$; ^1H NMR ($CDCl_3$): δ 7.38–7.18 (5H, m), 5.36 (1H, s), 4.18 (4H, q, *J* = 7 Hz), 4.07 (2H, d, *J* = 12 Hz), 3.68 (2H, d, *J* = 12 Hz), 2.71 (2H, s), 2.14 (2H, s), 1.22 (6H, t, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$): δ 172.0, 138.2, 129.2, 128.5, 126.2, 101.6, 75.5, 62.0, 47.4, 37.8, 31.8, 14.3. Anal. Calcd for $C_{19}H_{24}O_6$: C: 65.50; H: 6.94. Found: C: 65.51; H: 6.95.

7-Phenyl-6,8-dioxa-spiro[3,5]nonane-2,2-dicarboxylic acid (4)

Compound **3** (39.7 g, 0.11 mol) was added to a solution of potassium hydroxide 20.0 g, 0.30 mol) in ethanol (440 mL). The mixture was heated for 30 min at 80°C and then cooled to 0°C, and the precipitate of dipotassium salt of the title compound was filtered. This salt was then acidified with HCl to pH 4, and the mixture was extracted with ethyl acetate. The organic layer was dried and concentrated, and the residue was crystallized from petroleum ether to give compound **4** (27.1 g, 81%) as a white solid; mp 168.5–169.6°C; IR: 3047, 2717, 2683, 1741, 1709, 1459, 1309, 1101, 932, 902, 696; ESI-MS: *m/z* 291.05 $[(M-H)^-]$; ^1H NMR [dimethyl sulfoxide (DMSO)-d_6]: δ 12.61 (2H, s), 7.34–7.28 (5H, m), 5.36 (1H, s), 3.92 (2H, d, *J* = 12.0 Hz), 3.70 (2H, d, *J* = 12.0 Hz), 2.47 (2H, d, *J* = 20 Hz), 2.06 (2H, s). ^{13}C NMR (DMSO-d_6): δ 173.6, 139.2, 129.2, 128.6, 126.8, 101.0, 75.2, 47.6, 38.1, 32.2, 31.7. Anal. Calcd for $C_{15}H_{16}O_6$: C: 61.64; H: 5.52. Found: C: 61.63; H: 5.52.

7-Phenyl-6,8-dioxaspiro[3,5]nonane-2-carboxylic acid (5)

A solution of dicarboxylic acid **4** (8.0 g, 27.3 mmol) in pyridine (80 mL) was heated under reflux for 15 h and then concentrated *in vacuo*, and the residue was adjusted to pH 6 with 3 N hydrochloric acid. The product was extracted with ethyl acetate (3 × 100 mL), and the organic extracts were dried with anhydrous sodium sulfate and concentrated under reduced pressure to give **5** (6.7 g, 98%) as a white solid; mp 139.8–140.0°C; IR: 3067, 2955, 2939, 2769, 2676, 1693, 1497, 1454, 1090, 698 cm^{-1}; ESI-MS: *m/z* 249.05 $[(M+H)^+]$; ^1H NMR (DMSO-d_6): δ 11.90 (1H, s), 7.36–7.30 (5H, m), 5.38 (1H, s), 4.08 (1H, m), 3.91 (1H, m), 3.70–3.63 (2H, m), 3.03 (1H, t, *J* = 8.4 Hz), 2.44–2.30 (1H, m), 2.27–2.09 (1H, m), 1.77–1.74 (2H, m); ^{13}C NMR (DMSO-d_6): δ 176.9, 139.3, 129.2, 128.6, 126.7, 101.0, 75.8, 74.9, 34.2, 33.8, 32.2, 28.3. Anal. Calcd for $C_{14}H_{16}O_4$: C: 67.73; H: 6.50. Found: C: 67.73; H: 6.51.

2-*tert*-Butoxycarbonylamino-7-phenyl-6,8-dioxaspiro[3,5]nonane (6)

A solution of compound **5** (6.2 g, 0.025 mol) and Et_3N (3.02 g, 0.03 mol) in toluene (75 mL) was treated dropwise with DPPA (7.5 g, 27.5 mmol), and the mixture was heated at 95°C for 1 h. Then, tertiary butyl alcohol (5.5 g, 0.075 mol) was added, and the mixture was stirred for an additional 17 h, concentrated under reduced pressure, and treated with potassium hydroxide (40 mL, 10%). The product was extracted with ethyl acetate (3 × 50 mL), and the combined organic extracts were washed with water and saturated sodium chloride, dried with anhydrous sodium sulfate, and concentrated under reduced pressure to give a pink solid. The crude product was purified by column chromatography to obtain **6** (6.1 g, 76%); mp 137.6–137.9°C; IR: 3337, 2980, 2926, 2851, 1682, 1651, 1533, 1389, 1368, 1345, 1313, 1109, 748 cm^{-1}; ESI-MS: *m/z* 342.15 $[(M+Na)^+]$; ^1H NMR ($CDCl_3$): δ 7.43–7.22 (5H, m), 5.38 (1H, s), 4.68 (1H, s), 4.07–4.10 (2H, m), 3.91 (1H, m), 3.78–3.74 (2H, m), 2.72 (1H, m), 2.00 (1H, m), 1.84 (1H, m), 1.51 (1H, m), 1.47 (9H, s); ^{13}C NMR ($CDCl_3$): δ 138.3, 129.2, 128.5, 126.3, 101.7, 74.9, 39.3, 35.1, 31.7, 28.6. Anal. Calcd for $C_{18}H_{25}NO_4$: C: 67.69; H: 7.89, N: 4.39. Found: C: 67.71; H: 7.88, N: 4.36.

1-*tert*-Butoxycarbonylamino-3,3-bis(hydroxymethyl) cyclobutane (7)

A solution of compound **6** (3.2 g, 10 mmol) in methanol (50 mL) was treated with Pd (10% on charcoal, 0.6 g). The mixture was heated to 45°C under a hydrogen atmosphere (balloon) and stirred for 17 h, until the TLC results indicated the absence of compound **6**. The mixture was then cooled to room temperature and filtrated. The filtrate was concentrated under reduced pressure. The crude product was crystallized from petroleum ether to give **7** (2.3 g, 100%) as a white solid; mp 113.0–113.4°C; IR: 3373, 2977, 2932, 1682, 1526, 1390, 1366, 1171, 1042, 1026; ESI-MS: *m/z* 254.00 $[(M+Na)^+]$; ^1H NMR (DMSO-d_6): δ 6.92 (1H, d, *J* = 7.6 Hz), 4.45 (1H, t, *J* = 5.2 Hz), 4.33 (1H, d, *J* = 5.2 Hz), 3.78 (1H, q, *J* = 8.0 Hz), 3.29 (2H, d, *J* = 5.2 Hz), 3.21 (2H, d, *J* = 5.2 Hz), 1.91–1.88 (2H, m), 1.59–1.54 (2H, m), 1.30 (9H, s); ^{13}C NMR (DMSO-d_6): δ 155.2, 78.0, 66.6, 64.8, 34.5, 28.9. Anal. Calcd for $C_{11}H_{21}NO_4$: C: 57.12; H: 9.15, N: 6.06. Found: C: 57.13; H: 9.17, N: 6.09.

3-(*tert*-Butoxycarbonylamino)cyclobutane-1,1-diyl bis(methanesulfonate) (8)

Et_3N (2.09 mL, 15 mmol) was added to a solution of compound **7** (1.2 g, 5 mmol) in chloroform (10 mL). The mixture was cooled to -10°C, treated dropwise with mesyl chloride (0.93 mL, 12 mmol), returned to ambient temperature, stirred for 16 h, washed with water (1×20 mL), and extracted with dichloromethane (3 × 20 mL). The extract was washed with brine (1 × 20 mL), dried with sodium sulfate, and then concentrated under reduced pressure to give dimesylate **8** (2.0 g, 100%) as a white solid; mp 100.1–100.8°C; IR: 3345, 2988, 2944, 1681, 1646, 1539, 1353, 1287, 953, 814; ESI-MS: *m/z* 410.05 $[(M-H)^-]$; ^1H NMR ($CDCl_3$): δ 4.86 (1H, m), 4.24 (2H, s), 4.15 (2H, s), 4.10 (1H, s), 3.00 (6H, s), 2.34–2.29 (2H, m), 1.92–1.94 (2H, m), 1.37 (9H, s); ^{13}C NMR ($CDCl_3$): δ 155.1, 72.3, 70.6, 37.6, 35.8, 34.8, 28.6. Anal. Calcd for $C_{13}H_{25}NO_4S_2$: C: 40.30; H: 6.50, N: 3.61, S: 16.55. Found: C: 40.30; H: 6.50, N: 3.62: S: 16.51.

6-*tert*-Butoxycarbonylamino-2-thiaspiro[3,3]heptane (9)

A solution of compound **8** (2.4 g, 6.19 mmol) and $Na_2S{\cdot}9H_2O$ (1.62 g, 6.75 mmol) in DMSO (50 mL) was stirred at 80°C for 16 h, diluted with

petroleum ether, and the mixture was washed with water (1 × 20 mL) and brine (1 × 20 mL). The organic layer was dried with sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to give compound **9** (1.15 g, 81%) as a white solid; mp 93.8–94.6°C; IR: 3375, 2977, 2936, 1683, 1646, 1514, 1368, 1161, 624; ESI-MS: *m*/*z* 227.0 [(M-H)$^-$]; ^{1}H NMR ($CDCl_3$): δ 4.52 (1H, s), 3.90 (1H, s), 3.21 (2H, s), 3.11 (2H, s), 2.61 (2H, t, *J* = 8.0 Hz), 1.79 (2H, t, *J* = 9.6 Hz), 1.39 (9H, s); ^{13}C NMR ($CDCl_3$): δ 45.3, 42.0, 39.1, 38.1, 28.6. Anal. Calcd for $C_{11}H_{19}NO_2S$: C: 57.61; H: 8.35, N: 6.11, S: 13.98. Found: C: 57.62; H: 8.35, N: 6.13, S: 13.95.

6-Amino-2-thiaspiro[3,3]heptane hydrochloride (10)

A solution of compound **9** (0.9 g, 3.9 mmol) in a solution of HCl in ethyl acetate (2.5 M, 17 mL) was stirred at ambient temperature for 17 h, then concentrated under reduced pressure, washed with ether, and filtered. Concentration gave the title compound **10** (0.58 g, 87%) as a white solid; mp 241.7–243.8°C; IR: 2936, 2669, 2623, 2527, 2036, 1604, 1594, 1517, 1456, 1380, 1279; ESI-MS: *m*/*z* 129.90 [(M-HCl+H)$^+$]; ^{1}H NMR (DMSO-d_6): δ 8.3 (3H, s), 3.48–3.40 (1H, m), 3.16 (2H, s), 3.09 (2H, s), 2.47–2.42 (2H, m), 2.21–2.16 (2H, m); ^{13}C NMR (DMSO-d_6); δ 42.8, 41.4, 38.9, 38.3. Anal. Calcd for $C_6H_{12}ClNS$: C: 43.49; H: 7.30, N: 8.45, S: 19.35. Found: C: 43.48; H: 7.31, N: 8.44, S: 19.31.

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