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A convenient synthesis of 1′-*H*-spiro-(indoline-3,4′-piperidine) and its derivatives

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Abstract—A simple synthetic route has been developed to prepare 1′-*H*-spiro(indoline-3,4′-piperidine) (**1d**). Dialkylation of 2-fluorophenylacetonitrile with *N*-(*tert*-butyloxycarbonyl)-bis(2-chloroethyl)amine (**5**) gave **6**. Deprotection of Boc followed by cyclization resulted **1d** in 67% overall yield. Selective Boc or Cbz protection of 1′-*N* gave **1a** or **1b** with 90 and 85% yield, respectively. Thus, in a five-step procedure, **1a** and **1b** were synthesized from commercially available reagents in over 50% overall yield. All 3 compounds (**1a**, **1b** and **1d**) can be utilized as templates to synthesize compounds for GPCR targets.

1. Introduction

In the past few years, spiro-piperidines have received great attention because of their promising therapeutic application.[1–4] The spiro(indoline-3,4′-piperidine) scaffold is a key structural feature in **2** (MK-0677), a potent peptidomimetic growth hormone secretagogue (GHS);[5] **3**, a serine derived NK_1 antagonist;[6] and **4**, a potent and selective melanocortin subtype-4 (MC-4) receptor agonist.[7] It is also found in oxytocin, somatostatin, tachykinines, anaphylatoxin chemotactic receptor ligands, and is considered as a privileged structure for general G-protein coupled receptor (GPCR) ligands (Fig. 1).[8]

We were particularly interested in synthesizing multiple grams of 1′-*H*-spiro-(indoline-3,4′-piperidine) (**1d**), and its derivatives **1a** and **1b**, where the 1′-*N* is selectively protected by a Boc or Cbz group, respectively. These three compounds can all serve as convenient starting material for two-point diversity parallel synthesis. The only literature directly related to preparation of **1a** was reported by Chen et al.[9] involving a six-step synthesis which gave a low overall yield (<10%). Thus, this route was less attractive for large-scale synthesis.

Several methods have been published for the synthesis of other spiro(indoline-3,4′-piperidine) analogs. The Fischer indole type synthetic approach reported by Maligres et al. yielded **1b**, a 1′-Cbz-protected analog with an overall yield of 80% in five steps, but based on quantitative HPLC analysis only.[10] The two-step synthesis of 1′-methylated analog (**1c**) reported by Ong (Scheme 1) seemed to be straightforward;[11] however, in our hands, only a 20% overall yield was achieved. Subsequent 1′-*N*-demethylation with α-chloroethyl chloroformate (ACE-Cl)[12] also proved to be problematic, further limiting the use of this chemistry for our needs.[13] However, during the investigation of these routes, we identified an efficient method to generate **1d** using a modified approach for the synthesis of **1c**.

Our synthetic route is illustrated in Scheme 2. *N*-(*tert*-butyloxycarbonyl)-bis(2-chloroethyl)amine (**5**) was prepared from commercially available bis-(2-chloroethyl)-amine hydrochloride.[4] Dialkylation of 2-fluorophenyl-acetonitrile with **5** followed by deprotection of the Boc group afforded **7** in 70% yield.[2] Our initial attempt to prepare **7** directly from bis-(2-chloroethyl)amine hydrochloride without N-protection failed. Reduction of **7** with LAH and spontaneous cyclization gave **1d** in 95% yield. Finally, selective protection of **1d** at 1′-*N* with Boc_2O gave **1a** in 90% yield. Based on our experience, it was not successful to generate **1a** from **6** directly using LAH reduction because of concomitant reduction of the Boc group. In the meantime, **1b** was obtained by protection of **1d** with *N*-(benzyloxycarbonyloxy)succinimide (Z–OSu) in 85% yield.

In conclusion, we have developed a convenient synthesis of 1′-*H*-spiro-(indoline-3,4′-piperidine) (**1d**), which was obtained in 67% yield in four steps from commercially available reagents. Its versatile derivatives **1a** and **1b** were obtained in over 50% overall yield with an additional

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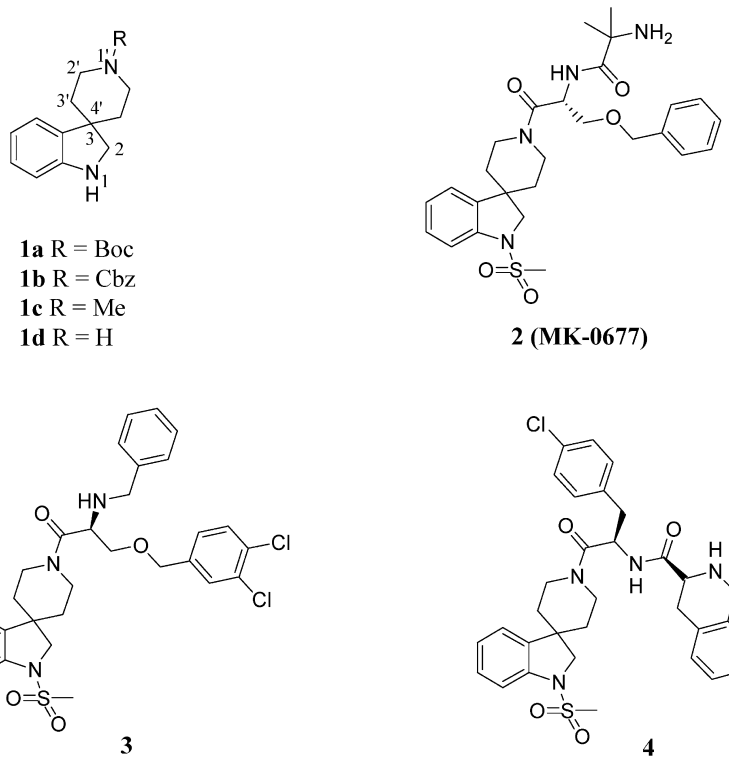
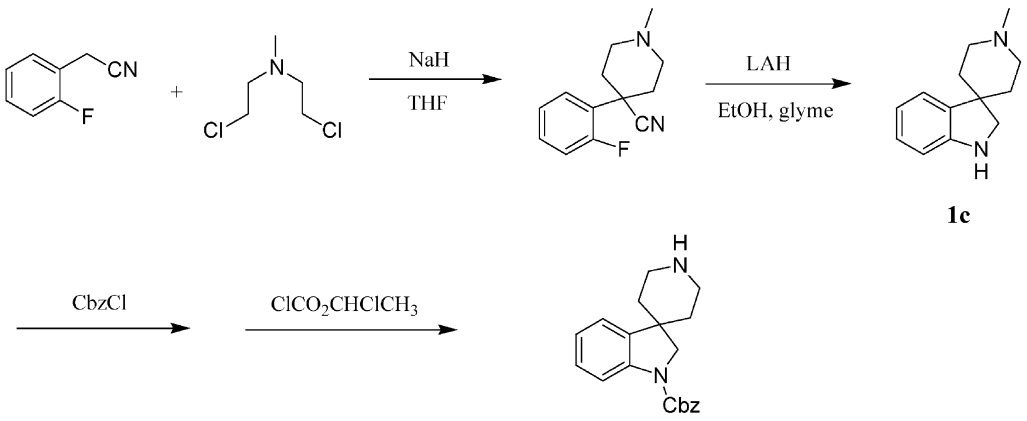


Figure 1.



Scheme 1.

selective protection step. All three compounds (**1a**, **1b** and **1d**) can be used in the parallel synthesis of compound libraries targeting GPCRs.[14]

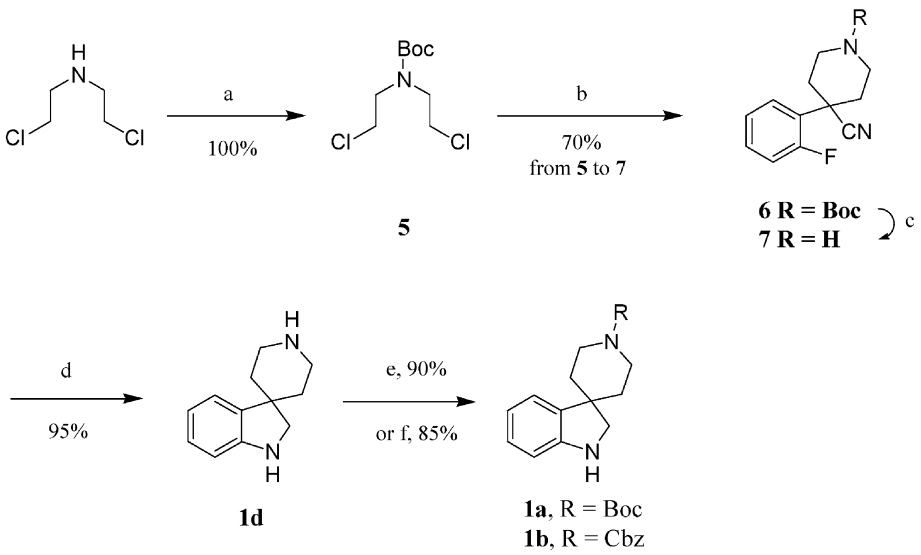
2. Experimental

2.1. General

^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on a Bruker AM 500 spectrometer in $CDCl_3$ solutions using TMS or $CDCl_3$ as the internal standard. CI mass spectra were performed with a PE API 2000 LC/MS/MS spectrometer. Elemental analyses were determined with a Perkin–Elmer 2400 series CHNS Analyzer. Melting points were observed with a Lab-Devices Mel-Temp II micro melting point apparatus (hot-plate type). EM Science silica gel 60 (230–400 mesh ASTM) was used for flash column chromatography. Anhydrous THF was distilled from sodium/benzophenone under nitrogen. All chemical reagents were purchased from Acros China.

2.2. Practical synthesis of 1′-*H*-spiro-[indoline-3,4′-piperidine] (1d) and its derivatives 1a and 1b

2.2.1. *N*-(*tert*-Butyloxycarbonyl)-bis(2-chloroethyl)-amine (5). The protection of bis-(2-chloroethyl)amine hydrochloride (42 g, 240 mmol) with di-*tert*-butyl dicarbonate (62 g, 280 mmol) was carried out based on the reference procedure.[4] The crude product was run through a pad of silica gel (petroleum ether/ethyl ether, 1:1) to yield **5** as a pale yellow oil (60 g, quantitative yield) (lit.[4] yield 88%). CI-MS *m/e* 242/244 (M+H).



Scheme 2. Reagents: (a) $(Boc)_2O/Et_3N$; (b) 2-fluorophenylacetonitrile/NaH/THF; (c) 8 M HCl/dioxane; (d) $LiAlH_4$/EtOH/glyme; (e) $Boc_2O/Et_3N/CH_2Cl_2$; (f) Z-OSu/THF.

2.2.2. 4-Cyano-4-(2-fluorophenyl)-1-*N*-(*tert*-butyloxycarbonyl)piperidine (6). To a solution of 2-fluorophenyl-acetonitrile (25 g, 180 mmol) in 300 mL anhydrous THF was added with vigorous stirring sodium hydride (60% in mineral oil) (47 g). The temperature of the reaction mixture was carefully kept below 5 °C. The ice water bath was removed after the addition, and the reaction mixture was allowed to warm to room temperature and stirred at the temperature for 30 min. The reaction mixture was then cooled to 0 °C and **5** (30 g, 120 mmol) was added. The reaction mixture was slowly warmed to reflux and then refluxed for 3 h. After refluxing, the reaction mixture was concentrated to remove the THF and to the recovered reaction mixture was added ice water slowly, followed by extraction with ether 3 times. The ether layers were combined and washed with water, dried with magnesium sulfate, filtered, and concentrated to yield the crude product as a yellow solid, which contained small amount of unreacted 2-fluorophenyl-acetonitrile. The yellow solid was recrystalized from ethyl acetate to give **6** as a white solid (48 g, 160 mmol). A small amount of analytical sample was prepared by purification of the above solid with a flash chromatography column and recrystalization: mp 120–122 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.47 (s, 9H), 2.08 (dd, 2H), 2.19 (d, J=12.3 Hz, 2H), 3.22 (m, 2H), 4.24 (m, 2H), 7.12 (dd, 1H), 7.18 (dd, 1H), 7.33–7.38 (m, 1H), 7.45 (dd, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.55, 33.98, 40.38, 41.01, 80.31, 117.2 (d, J=25 Hz), 120.4, 124.9, 126.5, 127.2, 130.5, 154.6, 160.9 (d, J=250 Hz); CI-MS *m/e* 305 (M+H). Anal. Calcd for $C_{17}H_{21}N_2O_2F$: C, 67.09; H, 6.95; N, 9.20. Found C, 67.09; H, 6.86; N, 9.23.

2.2.3. 4-Cyano-4-(2-fluorophenyl)piperidine (7). A mixture of **6** (48 g, 160 mmol) in dioxane-8 M HCl solution was refluxed for 30 min. The reaction mixture was concentrated to dryness and water (280 mL) was added. The mixture was washed with ether until no starting material could be detected by HPLC. The mixture was then adjusted to pH=9 and the aqueous layer was extracted by ether. The ether layers were combined, back washed with water, dried with magnesium sulfate, concentrated to dryness to give **7**, which was obtained as a white crystalline solid (17 g, 84 mmol, 70% from **5** to **7**): mp 96–98 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.08–2.14 (m, 2H), 2.22 (d, J=13.3 Hz, 2H), 3.14–3.20 (m, 4H), 7.12 (dd, 1H), 7.16 (dd, 1H), 7.31–7.36 (m, 1H), 7.45 (dd, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 35.03, 40.39, 43.72, 117.0 (d, J=25 Hz), 121.1, 124.8 (d, J=12.5 Hz), 127.1, 127.4, 130.1 (d, J=12.5 Hz), 160.9 (d, J=250 Hz); CI-MS *m/e* 205 (M+H). Anal. Calcd for $C_{12}H_{13}N_2F$: C, 70.57; H, 6.42; N, 13.72. Found C, 70.23; H, 6.32; N, 13.70.

2.2.4. 1′-*H*-Spiro-[indoline-3,4′-piperidine] (1d). To glyme (360 mL) was added LAH (15 g, 400 mmol). The reaction mixture was cooled to 0 °C and anhydrous ethanol (36 mL) was added slowly while keeping the reaction temperature around 0 °C. The ice bath was removed, and the mixture was slowly heated to reflux. To the above reaction mixture was added **7** (17 g, 84 mmol) in 200 mL glyme. The reaction mixture was refluxed for 72 h, cooled to 0 °C and water was slowly added with vigorous stirring. The precipitate was filtered, rinsed with dichloromethane a few times. The filtrates were combined, dried with anhydrous potassium carbonate, filtered, concentrated to dryness to give **1d** as a white crystalline solid (15 g, 80 mmol, 95%): mp 140–142 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.71 (d, 2H), 2.19 (d, J=13.3 Hz, 2H), 1.79 (dd, 2H), 2.74 (dd, 2H), 3.05 (d, J=12.6 Hz, 2H), 3.47 (s, 2H), 6.63 (d, J=7.7 Hz, 1H), 6.74 (dd, 1H), 7.04 (dd, 1H), 7.08 (d, J=7.41 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 36.85, 43.69, 44.85, 56.65, 109.7, 118.8, 122.7, 127.8, 137.3, 150.6; CI-MS *m/e* 189 (M+H). Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found C, 76.65; H, 8.52; N, 14.49.

2.2.5. 1′-Boc-spiro-[indoline-3,4′-piperidine] (1a). To a solution of **1d** (18.8 g, 100 mmol) in triethylamine (10 g, 100 mmol) and dichloromethane (250 mL) was slowly added a solution of di-*tert*-butyl dicarbonate (22 g, 100 mmol) in dichloromethane (250 mL). The reaction mixture was stirred at room temperature for 2 h, washed with saturated sodium bicarbonate solution and brine. The organic layer was dried with sodium sulfate, filtered and

concentrated to yield a crude solid. The solid was triturated with 50% ethyl acetate–hexane to give **1a** as a white solid (26 g, 90 mmol, 90%): mp 173–174 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.49 (s, 9H), 1.71 (d, J=13.1 Hz, 2H), 1.81 (m, 2H), 2.92 (m, 2H), 3.48 (s, 2H), 4.06 (m, 2H), 6.65 (d, J=7.5 Hz, 1H), 6.75 (dd, 1H), 7.03–7.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.65, 35.71, 41.20, 44.60, 56.10. 79.69, 109.9, 118.9, 122.8, 128.1, 136.5, 150.7, 155.1; CI-MS *m/e* 289 (M+H). Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found C, 70.49; H, 8.11; N, 9.55.

2.2.6. 1′-Cbz-spiro-[indoline-3,4′-piperidine] (1b). To a solution of **1d** (3.0 g, 16 mmol) in anhydrous THF (16 mL) was slowly added Z–OSu (4.0 g, 16 mmol). The reaction mixture was stirred at room temperature for 2 h, then concentrated to dryness. The crude product was partitioned between ethyl acetate and 1 N NaOH aqueous solution. The organic layer was then washed with saturated sodium bicarbonate solution and brine, dried with sodium sulfate, filtered and concentrated to yield a crude solid. The solid was triturated with MeOH to give **1b** as a white solid. (4.5 g, 14 mmol, 85%): mp 115–117 °C (lit.[10] mp 118–120 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.73–1.82 (m, 4H), 3.01 (m, 2H), 3.50 (s, 2H), 4.13 (m, 2H), 5.16 (s, 2H), 6.71 (d, J=7.8 Hz, 1H), 6.80 (dd, 1H), 7.32–7.38 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 35.56, 41.41, 44.51, 56.06, 67.24, 109.9, 118.9, 122.7, 128.0, 128.1, 128.6, 136.2, 137.0, 150.6, 155.5; CI-MS *m/e* 323.0 (M+H). Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found C, 74.38; H, 7.07; N, 8.59.

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References and notes

1. Palucki, B. L.; Feighner, S. D.; Pong, S.-S.; McKee, K. K.; Hrenick, D. L.; Tan, C.; Howard, A. D.; Van der Ploeg, L. H.; Patchett, A. A.; Nargund, R. P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1955–1957.
2. Dhar, T. G.; Nagarathnam, D.; Marzabadi, M. R.; Lagu, B.; Wong, W. C.; Chiu, G.; Tyagarajan, S.; Miao, S. W.; Zhang, F.; Sun, W.; Tian, D.; Shen, Q.; Zhang, J.; Wetzel, J. M.; Forray, C.; Chang, R.; Broten, T. P.; Schorn, T. W.; Chen, T. B.; O'Malley, S.; Ransom, R.; Schneck, K.; Bendesky, R.; Harrell, C. M.; Vyas, K. P.; Zhang, K.; Gilbert, J.; Pettibone, D. J.; Patane, M. A.; Bock, M. G.; Freidinger, R. M.; Gluchowski, C. *J. Med. Chem.* **1999**, *42*, 4778–4793.
3. Efange, S. M.; Kamath, A. P.; Khare, A. B.; Kung, M.-P.; Mach, R. H.; Parsons, S. M. *J. Med. Chem.* **1997**, *40*, 3905–3914.
4. Charmbers, M. S.; Baker, R.; Billington, D. C.; Knight, A. K.; Middlemiss, D. N.; Wong, E. H. *J. Med. Chem.* **1992**, *35*, 2033–2039.
5. Bednarek, M. A.; Feighner, S. D.; Pong, S.-S.; McKee, K. K.; Hreniuk, D. L.; Silva, M. V.; Warren, V. A.; Howard, A. D.; Van der Ploeg, L. H.; Heck, J. V. *J. Med. Chem.* **2000**, *43*, 4370–4376.
6. Elliott, J. M.; Broughton, H.; Cascieri, M. A.; Chicchi, G.; Huscroft, I. T.; Kurtz, M.; MacLeod, A. M.; Sadowski, S.; Stevenson, G. I. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1851–1856.
7. Nargund, R. P.; Sebhat, I.; Ye, Z.; Barakat, K.; Weinberg, D.; MacNeil, T.; Kalyani, R.; Martin, W.; Cashen, D.; Chen, H.; Drisko, J.; Mosley, R.; Fong, T.; Stearns, R.; Miller, R.; Tamvakopoulos, R.; Colwell, L.; Strack, A.; Shen, X.; Tan, C.; Pong, S. -S.; Howard, A.; Sailer, A.; Hickey, G.; MacIntyre, E.; Van der Ploeg, L.; Patchett, A. Abstracts of Papers, 222nd ACS National Meeting, Chicago, IL, US, August 26–30, 2001, MEDI-151.
8. (a) Bondensgaard, K.; Ankersen, M.; Thogersen, H.; Hansen, B. S.; Wulff, B. S.; Bywater, R. P. *J. Med. Chem.* **2004**, *47*, 888–899. (b) Patchett, A. A. *J. Med. Chem.* **2002**, *45*, 5609–5616.
9. Chen, M.-H.; Abraham, J. A. *Tetrahedron Lett.* **1996**, *37*, 5233–5234.
10. Maligres, P. E.; Houpis, I.; Rossen, K.; Molina, A.; Sager, J.; Upadhyay, V.; Wells, K. M.; Reamer, R. A.; Lynch, J. E.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron* **1997**, *53*, 10983–10992.
11. Ong, H. H.; Profitt, J. A.; Fortunato, J.; Glamkowski, E. J.; Ellis, D. B.; Geyer, H. M., III; Wilker, J. C.; Burghard, H. *J. Med. Chem.* **1983**, *26*, 981–986.
12. (a) Dean, D. C.; Nargund, R. P.; Pong, S.-S.; Chaung, L. P.; Griffin, P.; Melillo, D. G.; Ellsworth, R. L.; Van Der Ploeg, L. H.; Patchett, A. A.; Smith, R. G. *J. Med. Chem.* **1996**, *39*, 1767–1770. (b) Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081–2082.
13. Based on the in-house experiment, the 1′-*N*-demethylation using α-chloroethyl chloroformate (ACE–Cl) gave a complex reaction mixture with the desired product in 50% conversion based on HP LC/MS. The impurities were not identified.
14. Based on the in-house experiment, the 1′-*N* of **1d** can selectively react with acid chloride, acid anhydride, chloroformate and sulfonyl chloride. Thus, **1d** itself can be used as an useful template for parallel synthesis.