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Preparation of 3,4-fused-spiro[furan-5(5*H*),4′-piperidin]-2-one

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ABSTRACT

A general method for the preparation of various 3,4-fused-spiro[furan-5(5*H*),4′-piperidin]-2-one with high yield is reported. The formation of spiro[furanone-piperidine] structure was achieved by a Suzuki coupling, followed by an iodolactonization reaction.

Spiro piperidines are commonly used structure motifs in drug discoveries. One successful example is 1-(methylsulfonyl)-spiro[indoline-3,4′-piperidine] (**1**) employed by Merck scientists in the discovery of **MK-0677** which is one of the most potent peptidomimetic growth hormone secretagogues and entered Phase III clinical trials.[1] Recently we reported the synthesis of a close analogue to **1**, (2-methylsulfonyl)-2,3-dihydro-1*H*-spiro[isoquinoline-4,4′-piperidine] **2**, as an interesting intermediate for a medicinal chemistry program.[2]

We have had continuing interest in spiro piperidines, which led to the study of 3,4-pyridine fused-spiro[furan-5(5*H*),4′-piperidin]-2-one **3**, especially the structure **4**, 3-chloro-2-methyl-5*H*-spiro[furo[3,4-*b*]pyridine-7,4′-piperidin]-5-one (Fig. 1). We discovered **4** as an important common intermediate for the SAR study in one of our medicinal chemistry programs. Thus effort was invested in looking for a general synthesis of 3,4-fused-spiro[furan-5(5*H*),4′-piperidin]-2-one analogues.

The synthesis of 3,4-fused-spiro[furan-5(5*H*),4′-piperidin]-2-one was reported with benzo, pyridino, and thiopheno as fused rings.[3] Halogen-metal exchange or direct lithiation generates *ortho* carboxylate dianion, which is then added to N-protected 4-piperidinone, followed by acidic treatment to form the spiro lactone. This excellent chemistry provides one-pot reaction to form the 3,4-fused-spiro[furan-5(5*H*),4′-piperidin]-2-one in moderate yield. However, this method is limited to simple systems with no aromatic substitutions. Here we are reporting a general synthetic route we derived from the synthesis of compound **4**, utilizing a Suzuki coupling, followed by an iodolactonization reaction to form the spiro structure. The synthetic route for compound **4** is shown in Scheme 1.

Methyl 5-chloro-6-methyl-2-triflatepyridine-3-carboxylate **5**,[4] was coupled with *tert*-butyl 4-(4,4,5,5-tetramethyl-1,2,3-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate **6**[5] via a palladium-mediated high yield Suzuki cross-coupling to form **7**. Then the ester in **7** was hydrolyzed to acid to afford compound **8** in an excellent yield. An iodine initialized lactonization[6] under a basic condition in acetonitrile and water generated the spiro lactone structure **9**. Finally the iodo was removed by a radical type reduction using tributyltin hydride to provide 3-chloro-2-methyl-5*H*-spiro[furo[3,4-*b*]pyridine-7,4′-piperidin]-5-one **4** in 70% yield over four steps from compound **5**.[7]

The same synthetic route as for compound **4** was applied to different aromatic *ortho* halide or triflate carboxylic ester, or nitrile substrates for the preparation of different 3,4-fused-spiro[furan-5(5*H*),4′-piperidin]-2-ones. The reaction conditions for each step

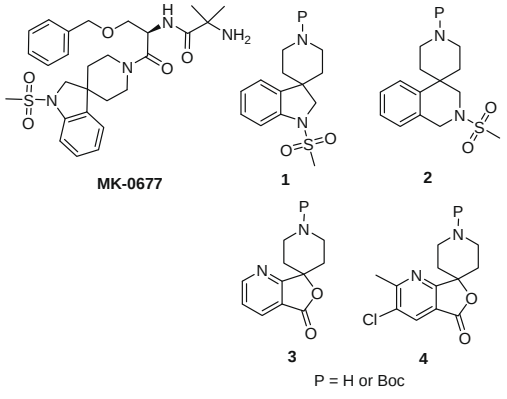

Figure 1.

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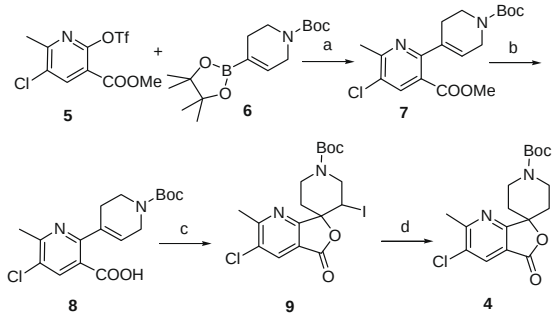
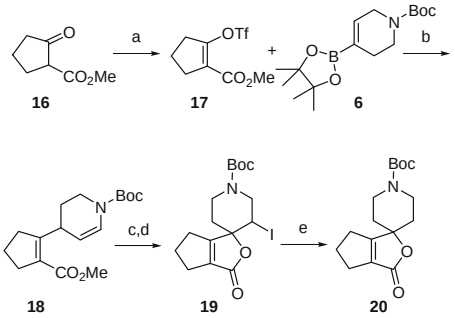
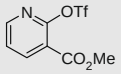
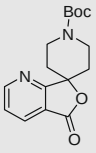
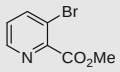
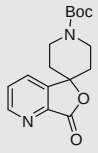
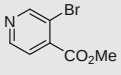
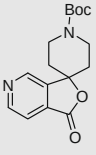
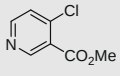
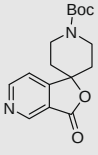
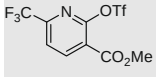
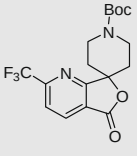
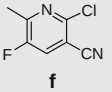
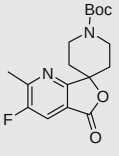
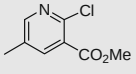
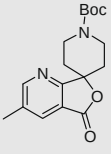
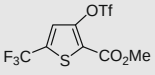
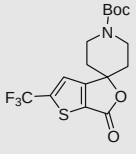
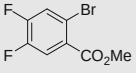
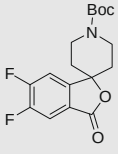
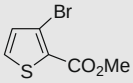
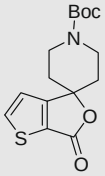


Scheme 1. Synthesis of **4**. Reagents and conditions: (a) Pd(dppf), Na_2CO_3, DMF/H_2O, 100 °C, microwave, 89%; (b) NaOH (5 N)/MeOH, then HCl, 95%; (c) I_2, KI, $NaHCO_3$, H_2O/CH_3CN (5/1), 85%; (d) Bu_3SnH, AIBN, toluene, 80 °C, 97%.



Scheme 2. Synthesis of **20**. Reagents and conditions: (a) Tf_2O, NaH, Et_2O, 0 °C, 97%; (b) Pd(dppf), Na_2CO_3, DMF/H_2O, 90 °C, 3 h, 94%; (c) NaOH(5 N)/MeOH, then HCl; (d) I_2, KI, $NaHCO_3$, H_2O/CH_3CN, 48% two steps; (d) Bu_3SnH, AIBN, toluene, 80 °C, 85%.

Table 1
3,4-Fused-spiro[furan-5(5*H*),4′-piperidin]-2-ones prepared from their corresponding aromatic substrates

Substrates	Products (yields)[a]	Substrates	Products (yields)[a]
 **a**	 **3a** (85%)	 **b**	 **3b** (48%)
 **c**	 **3c** (30%)	 **d**	 **3d** (43%)
 **e**	 **10** (70%)	 **f**	 **11** (31%)
 **g**	 **12** (45%)	 **h**	 **13** (30%)
 **i**	 **14** (64%)	 **j**	 **15** (54%)

[a] Overall yields are for four steps from substrates to spiro piperidines. Each product was prepared at the scale of 400 mg to multi grams.

of all compounds were exactly the same as those for **4**, and the overall yields were from moderate to good. The yields varied significantly on the step of iodolactonization which was sensitive to the substrates.[7] All final products as white solids were purified by chromatography and were characterized by LC–MS and ^{1}H NMR.[8] Table 1 lists the different commercially available or readily prepared substrates and the corresponding spiro piperidine products. The synthesis can tolerate different heterocyclic rings with various substitutions. In addition, we have applied this synthetic route to prepare a spiro[furan-5(5*H*)-4′-piperidin]-3-one with an olefinic fused ring such as compound **20** (Scheme 2). Ethyl 2-oxocyclopentanecarboxylate **16** was converted to enol triflate **17** when treated by triflic anhydride in ether with sodium hydride as a base. Suzuki coupling of **17** with **6** catalyzed by Pd(dppf) generated product **18**. Hydrolysis of ester in **18** followed by iodo lactonization converted it to a spiro compound **19**. Finally, the iodo was reduced by tributyltin hydride under radical condition to form the spiro compound **20**[8] with an unsaturated fused ring.

Effort to expand the furan ring to a six-membered lactone was not successful. Homologation of acid **8** led to an aryl acetic acid. However to our disappointment, iodolactonization on this homologated acid to form the six-membered lactone did not work. Presumably the formation of a six-membered lactone is much slower than the formation of a five-membered ring, which led to a complicated mixture of iodination products unable to be characterized.

In summary, we have demonstrated that the biologically interesting 3,4-fused-spiro[furan-5(5*H*),4′-piperidin]-2-one can be prepared from aromatic *ortho* halide or triflate carboxylic ester, or nitrile via a Suzuki coupling and an iodolactonization as key steps. This methodology allows for a variety of aromatic or olefinic fused rings with various substitutions. The piperidine nitrogen and the lactone functional groups in the spiro structures can be used as handles for further derivatizations for the preparation of biologically active molecules.

Acknowledgments

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4. Compound **5** was readily prepared from commercially available 2-hydroxy-6-methyl-nictinic acid by chlorination, esterification and conversion of 2-hydroxy to triflate: Cale, A. D.; Gero, T. W.; Walker, K. R.; Lo, Y. S.; Welstead, W. J.; Jaques, L. W.; Johnson, A. F.; Leonard, C. A.; Nolan, J. C.; Johnson, D. N. *J. Med. Chem.* **1989**, *32*, 2178.
5. Compound **6** was prepared following the literatures: (a) Eastwood, P. R. *Tetrahedron Lett.* **2000**, *41*, 3705; (b) Wustrow, D. J.; Wise, L. D. *Syntheis* **1991**, 993.
6. (a) Mali, R. S.; Patil, S. R. *Synth. Commun.* **1990**, *20*, 167; (b) Reich, S. H.; Melnick, M.; Pino, M. J.; Fuhry, M. M.; Trippe, A. J.; Appelt, K.; Davies, J. F.; Wu, B.-W.; Musick, L. *J. Med. Chem.* **1996**, *39*, 2781.
7. *General procedures for the preparation of* **4**: (a) Suzuki cross-coupling to **7**: A dried heavy-wall pyrex vessel was charged with **5** (2.68 g, 8.04 mmol), Pd(dppf) (0.294 g, 0.4 mmol), **6** (2.487 g, 8.04 mmol), sodium carbonate (2.588 g, 24.1 mol), H_2O (4 mL), and DMF (12 mL). The reaction mixture was flushed with nitrogen and the vessel was sealed before mixing with a Biotage microwave reactor. The reaction mixture was exposed to microwave irradiation for 1 h at 100 °C. After cooled down to room temperature, the mixture was partitioned between ethyl acetate (20 mL) and water (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic phases were washed with water, brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by MPLC (40 g silica gel, 0–20% ethyl acetate in hexanes) to afford white solid product **7** 2.63 g (89%, R_f = 0.2 by ethyl acetate:hexanes = 1:4). $C_{18}H_{23}ClN_2O_4$: LC–MS, ESI $(M+H)^+$: 367.2; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.99 (1H, s), 5.71 (1H, s), 4.03 (2H, d, J = 2.5 Hz), 3.83 (3H, s), 3.63 (2H, br), 2.63 (3H, s), 2.46 (2H, d, J = 1.5 Hz), 1.46 (9H, s) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.8, 163.3, 158.9, 154.1, 153.8, 152.0, 137.9, 130.5, 123.9, 82.5, 52.3, 43.6, 28.1, 27.9, 27.7, 22.5 ppm; (b) hydrolysis of ester to acid **8**: To a 100 mL one-necked round-bottomed flask was charged **7** (4.55 g, 12.40 mmol) along with MeOH (15 mL) and NaOH (5 N, 8 mL). The resulting reaction mixture was stirred and heated to 60 °C for 1 h. Then the reaction mixture was concentrated to half volume. After the mixture was acidified to pH 3 by concentrated HCl, the mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic phases were washed with water, brine, dried over $MgSO_4$, filtered, and concentrated to afford light colored solid product **8** 4.376 g (100%). $C_{17}H_{22}ClN_2O_4$: LC–MS, ESI $(M+H)^+$: 353.2; (c) iodolactonization to **9**: To a 500 mL one-necked round-bottomed flask was charged **8** (4.376 g, 12.40 mol) and CH_3CN (30 mL), $NaHCO_3$ (satd, 150 mL). Most of the acid dissolved. Under stirring, a solution of I_2 (4.092 g, 16.124 mmol) and KI (10.295 g, 62.015 mmol) in water (60 mL) was added dropwise in 10 min. The resulting reaction mixture was stirred at room temperature for 18 h overnight. Most of the iodine color paled away. To the flask, ethyl acetate (100 mL) was added, followed by a solution of NaS_2O_3 (15%, 60 mL). The solution was stirred for 20 min and became colorless. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic phases were washed with water, brine, dried over $MgSO_4$, filtered, and concentrated to afford light color product **9** 5.00 g (85%, R_f = 0.4 in ethyl acetate:hexanes = 1:4). $C_{17}H_{20}ClIN_2O_4$: LC–MS, ESI $(M+Na)^+$: 501.0; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.11 (1H, s), 2.78 (3H, s), 2.38 (1H, dd, J = 12.5, 9.0 Hz), 4.62 (1H, br), 4.42 (1H, dd, J = 12.0, 4.5 Hz), 4.02–4.30 (3H, br), 3.82 (1H, br),2.15 (1H, d, J = 6.5 Hz), 1.53 (9H, s) ppm; (d) reduction of iodo in **9** to **4**: To a 500 mL one-necked round-bottomed flask was charged **9** (5.00 g, 10.44 mmol), AIBN (0.086 g, 0.052 mmol), and toluene (40 mL). The mixture was heated to 80 °C and stirred while Bu_3SnH (9.00 g, 30.93 mmol) was added by syringe dropwise under nitrogen. The mixture was stirred and heated in an oil bath of 80 °C for 3 h, and then concentrated. The residue was purified by MPLC (330 g silica gel, 0–25% ethyl acetate in hexanes) to afford white solid product **4** 3.56 g (96.6%, R_f = 0.3 in ethyl acetate:hexanes = 1:4). $C_{17}H_{21}ClN_2O_4$: LC–MS, ESI $(M+Na)^+$: 375.2; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.07 (1H, s), 4.20 (2H, br, 3.28 (2H, br), 2.75 (3H, s), 2.23 (2H, td, J = 13.5, 5.0 Hz), 1.64 (2H, d, J = 12.0 Hz), 1.49 (9H, s) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.2, 165.8, 163.0, 153.9, 133.4, 132.2, 118.0, 84.8, 79.4, 40.3 (br), 39.8 (br), 33.4, 28.0, 23.4 ppm.
8. *Compound* **3a**:$C_{16}H_{20}N_2O_4$: LC–MS, ESI $(M+Na)^+$: 327.1; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.77 (1H, dd, J = 6.0, 1.0 Hz), 8.12 (1H, dd, J = 7.0, 1.5 Hz), 7.43 (1H, dd, J = 7.5, 5.0 Hz), 4.12 (2H, m), 3.21 (2H, m), 2.19 (2H, m), 1.61 (2H, d, J = 14.0 Hz)), 1.42 (9H, s) ppm; **3b**: $C_{16}H_{20}N_2O_4$: LC–MS, ESI $(M+Na)^+$: 327.1; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.89 (1H, d, J = 4.5 Hz), 7.79 (1H, dd, J = 8.0, 1.0 Hz), 7.56 (1H, dd, J = 8.0, 4.5 Hz), 4.19 (2H, br), 3.27 (2H, br), 2.07 (2H, m), 1.69 (2H, d, J = 13.5 Hz), 1.48 (9H, s) ppm; **3c**: $C_{16}H_{20}N_2O_4$: LC–MS, ESI $(M+Na)^+$: 327.1; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.88 (1H, d, J = 4.5 Hz), 8.86 (1H, s), 7.79 (1H, d, 4.5 Hz), 4.23 (2H, br), 3.28 (2H, br), 2.15 (2H, m), 1.76 (2H, d, J = 14.0 Hz), 1.51 (9H, s) ppm; **3d**: $C_{16}H_{20}N_2O_4$: LC–MS, ESI $(M+Na)^+$: 327.1; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.20 (1H, s), 8.98 (1H, s, J = 2.0 Hz), 7.39 (1H, d, J = 2.0 Hz), 4.21 (2H, br), 3.25 (2H, br), 2.08 (2H, m), 1.72 (2H, d, J = 13.5 Hz), 1.49 (9H, s) ppm; **10**: $C_{17}H_{19}F_3N_2O_4$: LC–MS, ESI $(M+Na)^+$: 395.1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.39 (1H, 8.0 Hz), 7.88 (1H, d, 8.0 Hz), 4.25 (2H, br), 3.31 (2H, br), 2.33 (2H, m), 1.72 (2H, d, J = 13.6 Hz), 1.50 (9H, s) ppm; **11**: $C_{17}H_{21}FN_2O_4$: LC–MS, ESI $(M+Na)^+$: 359.2; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.72 (1H, d, J = 7.5 Hz), 4.19 (2H, br), 3.28 (2H, br), 2.65 (3H, s), 2.25 (2H, m), 1.64 (2H, br), 1.49 (9H, s) ppm; **12**: $C_{17}H_{22}N_2O_4$: LC–MS, ESI $(M+Na)^+$: 341.2; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.64 (1H, s), 7.95 (1H, s), 4.19 (2H, br), 3.29 (2 h, br), 2.46 (3H, s), 2.22 (2H, m), 1.62 (2H, d, J = 13.5 Hz), 1.46 (9H, s) ppm; **13**: $C_{16}H_{18}F_3NO_4S$: LC–MS, ESI $(M+Na)^+$: 400.1; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.35 (1H, s), 4.09 (2H, br), 3.31 (2H, br), 2.02 (2H, m), 1.80 (2H, d, J = 13.0 Hz), 1.47 (9H, s) ppm; **14**: $C_{17}H_{19}F_2NO_4$: LC–MS, ESI $(M+Na)^+$: 362.2; ^{1}H NMR (CD_3OD, 500 MHz) δ: 7.79 (1H, dd, J = 8.5, 7.0 Hz), 7.70 (1H, 9.0, 7.0 Hz), 4.22 (2H, d, J = 13.0 Hz), 3.21 (2H, br), 2.20 (2H, m), 1.71 (2H, d, J = 13.5 Hz), 1.51 (9H, s) ppm; **15**: $C_{15}H_{19}NO_4S$: LC–MS, ESI $(M+Na)^+$: 332.1; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.83 (1H, d, J = 5.0 Hz), 6.98 (1H, d, 5.0 Hz), 4.06 (2H, br), 3.34 (2H, br), 2.02 (2H, m), 1.80 (2H, d, J = 14.0 Hz), 1.49 (9H, s) ppm; **20**: $C_{16}H_{23}NO_4$: LC–MS, ESI $(M+Na)^+$: 316.1; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.06 (2H, br), 3.21 (2H, br), 2.52 (4H, br), 2.46 (2H, br), 1.83 (2H, m), 1.58 (2H, d, J = 13.0 Hz), 1.46 (9H, s) ppm.