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Synthesis of 4-substituted 4-arylpiperidines

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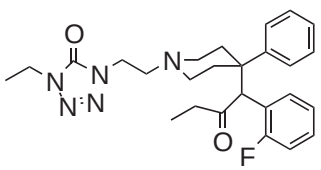
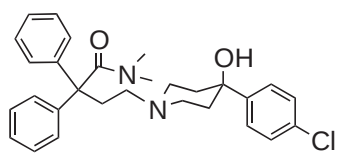
Abstract

Several novel 4-substituted 4-arylpiperidines were synthesized. The chemistry leading to 4-(4-chlorophenyl)-4-fluoropiperidine (**6**), 4-azido-4-(4-chlorophenyl)piperidine (**7**) and 4-(4-chlorophenyl)-4-methylpiperidine (**8**) is described. © 2000 Elsevier Science Ltd. All rights reserved.

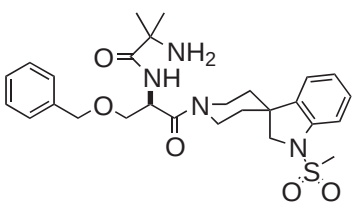
4-Arylpiperidines are important functionalities found in several biologically active molecules. Examples of such molecules include the analgesic Trefentanil (**1**),[1] the antidiarrheal Loperamide (**2**),[2,3] the growth hormone secretagogue MK0677 (**3**)[4] and the smooth muscle relaxant Anileridine (**4**)[5] (Fig. 1).



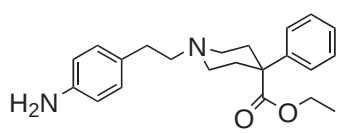
Trefentanil (**1**)



Loperamide (**2**)



MK0677 (**3**)



Anileridine (**4**)

Figure 1.

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In our small molecule drug discovery efforts we targeted the synthesis of several 4-substituted 4-arylpiperidines. One of the most common 4-arylpiperidines found in biologically active molecules is 4-(4-chlorophenyl)-4-hydroxypiperidine (**5**). This motif is also one of the most widely found pharmacophores utilized in G-protein coupled receptor (GPCR) antagonists. We decided to introduce substituents at the C-4 position with both hydrogen bonding capabilities as well as hydrophobic substituents. We herein report on the synthesis of the following 4-substituted 4-arylpiperidines: 4-(4-chlorophenyl)-4-fluoropiperidine (**6**), 4-azido-4-(4-chlorophenyl)-piperidine (**7**) and 4-(4-chlorophenyl)-4-methylpiperidine (**8**) (Fig. 2). This is the first reported synthesis of a 4-fluoro- and 4-azido-4-arylpiperidine.

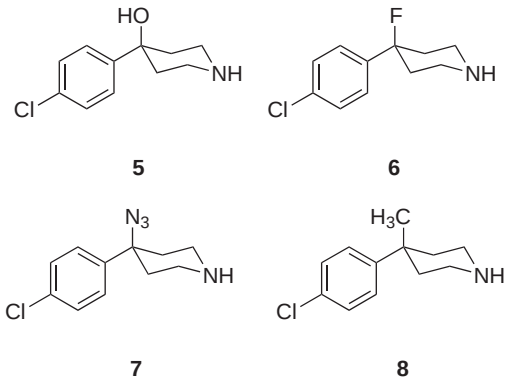
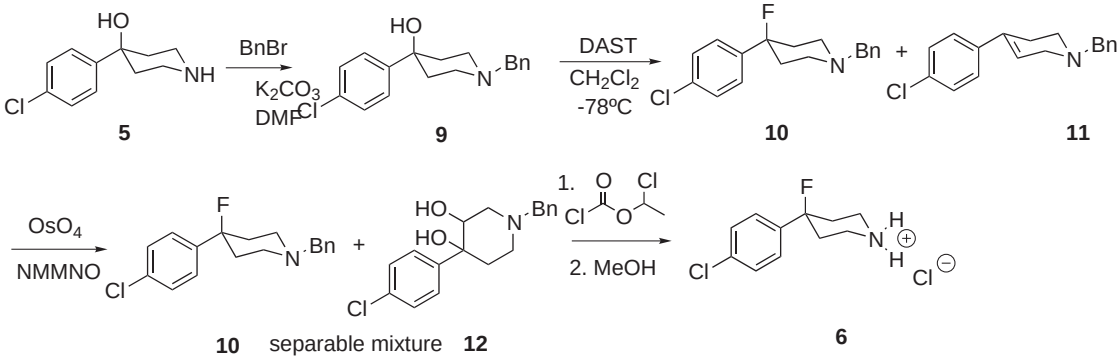


Figure 2.

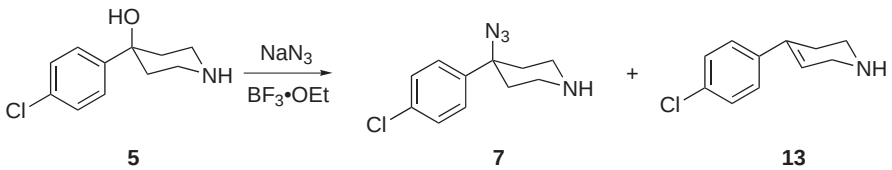
The synthesis of 4-(4-chlorophenyl)-4-fluoropiperidine (**6**) began utilizing commercially available 4-(4-chlorophenyl)-4-hydroxypiperidine (**5**, Scheme 1). Protection of the piperidine nitrogen as its *N*-benzylamine proved necessary for ease of purification. Benzylation of **5** was accomplished utilizing benzyl bromide (1.1 equiv.) and K_2CO_3 (2 equiv.) in DMF[6] at rt overnight producing **9** in 89% yield. Conversion of the benzylic hydroxyl group to the benzylic fluoride, **10**, was effected in the presence of diethylaminosulfur trifluoride (DAST, 1.2 equiv.) at −78°C in methylene chloride.[7–9] This reagent was selected as the hydroxyl group at C4 is both benzylic and tertiary. This allows for Lewis acid mediated carbocation chemistry to be more successful. Unfortunately, the Lewis acid also promotes formation of an olefin through the carbocation intermediate. This reaction resulted in a quantitative conversion of **9** to an inseparable 1:1



Scheme 1.

mixture of fluoropiperidine **10** and 4-(4-chlorphenyl)tetrahydropyridine **11**. Several unsuccessful attempts were made to influence the ratio of desired to undesired product formation including changes in temperature, stoichiometry of reagents and solvents utilized. In order to separate out the desired product, the mixture of **10** and **11** was subjected to catalytic osmium tetroxide oxidation (0.05 equiv. OsO_4, 1.1 equiv. *N*-methylmorpholine *N*-oxide, rt, overnight).[10] This resulted in the dihydroxylation of the undesired **11** to **12** allowing the clean separation of the desired fluoropiperidine **10** from the byproduct. Deprotection of **10** was accomplished using 1-chloroethylchloroformate (1.1 equiv. in CH_2Cl_2, rt, 1 h).[11] Excess 1-chloroethylchloroformate and CH_2Cl_2 was removed under reduced pressure. The resulting carbamate was then converted to the final desired product by refluxing the crude residue in methanol for 1 h. This two-step process resulted in the quantitatively conversion of **10** to the hydrochloride salt **6**.

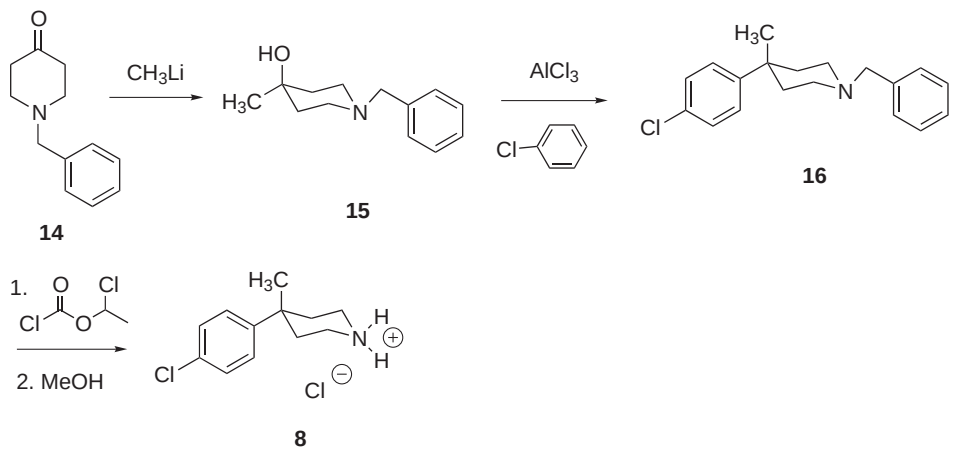
The synthesis of 4-azido-4-(4-chlorophenyl)piperidine (**7**) also began with piperidine **5** (Scheme 2). Reaction of **5** in the presence of NaN_3 (1.2 equiv.) and $BF_3{\cdot}OEt_2$ (1.1 equiv.) in anhydrous dioxane at 0°C[12,13] led to the formation of the azidopiperidine **7** and olefin **13** in a one to three ratio. This mixture proved to be separable and resulted in the isolation of **7** in 25% yield.



5 **7** **13**

Scheme 2.

The synthesis of 4-(4-chlorophenyl)-4-methylpiperidine (**8**) began with the addition of commercially available 1-benzyl-4-oxopiperidine (**14**) to a cold (−78°C) stirred solution of 1.0 M methyllithium in diethyl ether (1.2 equiv.)[14] (Scheme 3). Tertiary alcohol **15** was isolated in 51% yield after flash column chromatography.



14 **15** **16** **8**

Scheme 3.

The order of addition proved to be critical here, as addition of the alkyl lithium reagent to a solution of **14** resulted in the formation of adduct **17** in 55% yield (Fig. 3). No desired product was detected. This product is presumably generated from benzylic deprotonation followed by 1,2-addition to the ketone. Friedel–Crafts arylation[15] of the tertiary alcohol in the presence of chlorobenzene (neat) and aluminum trichloride (1.1 equiv.) resulted in the formation of **16** (88% yield). Debenzylation utilizing the chloroformate methodology mentioned above[16] smoothly produced the desired piperidine hydrochloride salt **8** quantitatively.

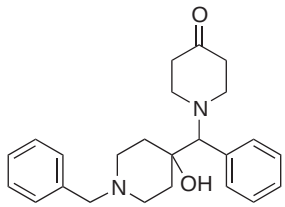


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Figure 3.

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16. All compounds were characterized via NMR (Bruker AC 250) and LC/MS (Micromass Platform LCZ with electrospray ionization and diode array LC detection at 200–400 nm). 4-(4-Chlorophenyl)-4-fluoropiperidine·HCl (**6**): ^{1}H NMR (DMSO-d_6): δ 2.09 (bt, 2H, $J=13$ Hz), 2.36 (dt, 1H, $J=7.5$, 13 Hz), 2.36 (dt, 1H, $J=7.5$, 13 Hz), 2.49 (dt, 1H, $J=7.5$, 13 Hz), 3.11 (bt, 2H, $J=13$ Hz), 3.32 (m, 2H), 7.41 (d, 2H, $J=7.5$ Hz), 7.51 (d, 2H, $J=7.5$ Hz); MS: [M+] 214. 4-Azido-4-(4-chlorophenyl)piperidine (**7**): ^{1}H NMR (DMSO-d_6): δ 1.71 (m, 2H), 2.04 (m, 2H), 3.00 (m, 4H), 3.33 (bs, 1H, NH), 7.42 (bs, 4H); MS: [M+1−N_2] 212. 4-(4-Chlorophenyl)-4-methylpiperidine·HCl (**8**): ^{1}H NMR ($CDCl_3$): δ 1.31 (s, 3H), 1.88–2.00 (m, 2H), 2.30–2.41 (m, 2H), 2.97–3.09 (m, 2H), 3.22–3.34 (m, 4H), 7.32–7.43 (m, 4H); MS: [M+] 210.