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Syntheses of fluorinated phencyclidine analogs

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Abstract

Syntheses of several fluorinated phencyclidine (PCP) analogs are described. These compounds are being used to probe PCP binding sites on *N*-methyl-D-aspartate (NMDA) receptors. The compounds were prepared in good yields by Grignard reaction of appropriate fluorine substituted bromobenzene with carbonitrile intermediates. Syntheses of the known compound 1-[1-(3-fluorophenyl)cyclohexyl]piperidine, and the novel compounds 1-[1-(4-fluorophenyl)cyclohexyl]piperidine, 1-[1-(3-fluorophenyl) cyclohexyl]pyrrolidine, and 1-[1-(4-fluorophenyl)cyclohexyl]pyrrolidine are reported.

Keywords: Fluorinated phencyclidine analogs; Synthesis; Characterization; Grignard reaction; Carbonitrile

1. Introduction

Substitution of a hydrogen atom with fluorine in biologically active molecules is known to affect the biological activities of such molecules [1–5]. As part of our efforts to obtain selective non-competitive antagonists at the PCP binding site on NMDA receptor complex, we have prepared analogs of phencyclidine with fluorine on the aromatic ring, including at *o*- and *p*-positions. Also, we have prepared fluorinated analogs where the piperidine ring of phencyclidine is replaced with a more constrained pyrrolidine ring to examine effects of conformational restriction on pharmacological activities. Incorporation of fluorine on the aromatic ring of each molecule is anticipated to have pronounced effects on electron distribution and dipole moments within each molecule because of fluorine's high electronegativity. In addition, it can function as a hydrogen bond acceptor as a consequence of available electron density. As part of our continuing interest in syntheses of fluorinated aromatic amines of biological interest [6–9], we describe herein syntheses of 1-[1-(3-fluorophenyl)cyclo-hexyl]-piperidine (**3**), 1-[1-(4-fluoro phenyl)cyclohexyl]piperidine (**4**), 1-[1-(3-fluoro- phenyl)cyclohexyl]pyrrolidine (**5**), and 1-[1-(4-fluorophenyl)cyclohexyl]pyrrolidine (**6**) Schemes 1 and 2.

2. Results and discussion

Ring-fluorinated compounds **3**–**5**, and **6** were synthesized by a modification of the method of Maddox et al. [10] involving reaction of substituted Grignard reagents with carbonitriles. Appropriate dihalogenated benzenes were each reacted with magnesium to form Grignard reagents which were then reacted with appropriate carbonitriles. Reactions between the Grignard reagents and the carbonitriles were slow and incomplete. In a bid to rectify this, molar ratio of Grignard reagent to carbonitrile was increased to be at least 3–1. Even then, there were still significant quantities of unreacted carbonitriles in the reaction products and yields were low. Long reaction times were then resorted to, but these gave problems as side-products which were not easy to remove were formed in large quantities. Such side products are not uncommon and have been reported in literature [11]. The procedures being reported gave desired products in reasonable yields, 25–65%.

The mechanism of the reaction would seem to explain the copious amounts of side products formed. Nitrile is a good leaving group hence it would be easily removed from the quaternary carbon of the carbonitrile, particularly with effects the neighboring nitrogen will have on stabilizing resulting tertiary carbocation. The S_N1 attack of the Grignard reagent on the carbocation is complicated by the neighboring piperidine or pyrrolidine which can form enamine or imine. The reactivities of these groups could contribute significantly to formation of side products observed.

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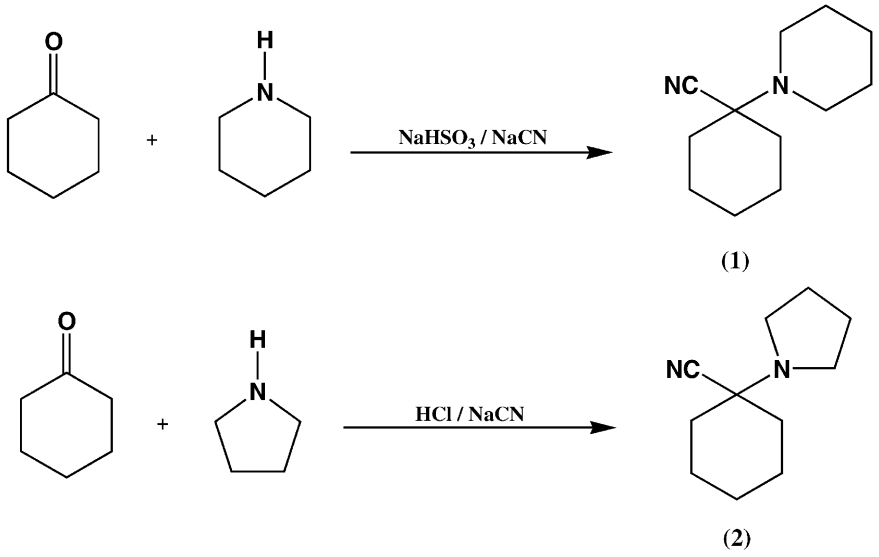
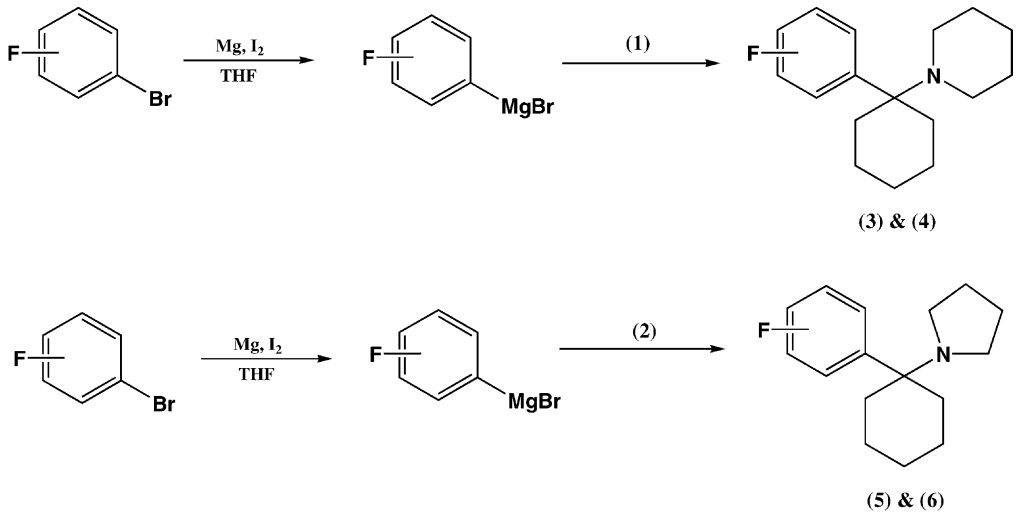


Scheme 1. Synthesis of intermediates (**1**) and (**2**).



Scheme 2. Synthesis of target compounds. For compounds (**3**) and (**5**), fluorine is at the *m*-position while for compounds (**4**) and (**6**), it is at the *p*-position.

3. Experimental

3.1. Materials

3-Bromofluorobenzene (99%), 4-bromofluorobenzene (99%), cyclohexanone (99.8%), piperidine (99%), pyrrolidine (>99%), $NaHSO_3$ (Acros), NaCN (Aldrich), ammonium hydroxide (28–30%), diethyl ether, HCl, H_2SO_4, and THF (Fisher) magnesium turnings, and NaCl. THF was distilled over sodium prior to use, under a dry nitrogen atmosphere.

3.2. Instrumentation and methods

Melting points were determined on a Mel-Temp II capillary melting point apparatus. IR spectra were recorded on a Perkin-Elmer 16 PC FT-IR spectrophotometer. MS spectra were obtained by electrospray method using the Finnigan TSQ-700 mass spectrometer. NMR spectra were obtained on a Varian 300/54 300 MHz spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$and referenced to internal TMS (0 ppm) and $CDCl_3$ (77 ppm) signals, respectively. ^{19}F NMR spectra were obtained in $CDCl_3$ and referenced to $CFCl_3$ as internal standard (0 ppm). All values reported are δ values in parts per million. Elemental analyses were performed by Galbraith laboratories, Knoxville, TN, and observed values were within $\pm 0.4\%$ of theoretical values. Column chromatographic separations were performed over Acros silica gel no. 7631-86-9 particle size 35–70 μm. Preparative TLC separations were performed on Analtech Uniplate silica gel GF 20 cm × 20 cm TLC plates.

3.3. Preparation of 1-piperidinocyclohexanecarbonitrile (**1**)

To a solution of sodium bisulfite (11.5 g, 0.11 mol) in 25 ml of water was added 9.8 g (0.1 mol) of cyclohexanone. A solution of 5.4 g (0.11 mol) of sodium cyanide and 8.5 g (0.1 mol) piperidine in 20 ml water was then added and the reaction allowed to stir overnight at room temperature. The product was filtered off, washed with water, and dried under vacuum to give 15.92 g (82.1%) of a white crystalline solid, mp 65–67 °C.

IR ($CHCl_3$) cm^{-1}: 2230 (C≡N); ^1H NMR ($CDCl_3$): 2.7–1.1 (b, 20H, $10CH_2$); ^{13}C NMR ($CDCl_3$): 120 (s, 1C, CN); 61 (s, 1C, 4 °C); 48 (s, 2C, $2CH_2$); 34 (s, 2C, $2CH_2$); 27 (s, 2C, $2CH_2$); 25 (s, 1C, CH_2); 24 (s, 1C, CH_2); 22 (s, 2C, $2CH_2$); MS ESI (*m/z*, species, %): 166, $[M - CN]^+$, 100; 193, $[M + H]^+$, 57.

3.4. Preparation of 1-pyrrolidinocyclohexanecarbonitrile (**2**)

35% Hydrochloric acid (5.0 ml, 0.051 mol) was slowly added to a mixture of pyrrolidine (3.63 g, 0.051 mol) and ice 30 g. Cyclohexanone (5.0 g, 0.051 mol) was added to the mixture. A solution of sodium cyanide (2.75 g, 0.056 mol) in 15 ml water was then added dropwise while stirring vigorously. The reaction was stirred at room temperature overnight and extracted with chloroform (2 ml × 20 ml). The chloroform extract was dried over sodium sulfate and the solvent evaporated to obtain 8.0 g (88%) of a yellowish oil.

IR ($CHCl_3$) cm^{-1}: 2250 (C≡N); ^1H NMR ($CDCl_3$): 2.7–1.2 (b, 18H, $9CH_2$); ^{13}C NMR ($CDCl_3$): 120 (s, 1C, CN); 61 (s, 1C, 4 °C); 48 (s, 2C, $2CH_2$); 36 (s, 2C, $2CH_2$); 25 (s, 1C, CH_2); 23 (s, 2C, $2CH_2$); 21 (s, 2C, $2CH_2$).

3.5. Preparation of 1-[1-(3-fluorophenyl)cyclohexyl]-piperidine (**3**)

A mixture of 3-bromofluorobenzene (3.0 g, 0.017 mol), magnesium turnings (1.7 g, 0.068 mol), and a few crystals of iodine in 10 ml THF were stirred vigorously under nitrogen at room temperature for 2 h. After this, a solution of nitrile **1** (3.26 g, 0.017 mol) in 15 ml THF was added dropwise, and the reaction stirred overnight at room temperature. The reaction was quenched carefully with water and extracted with ether (3 ml × 20 ml). The ether extracts were combined and extracted with 2N HCl (3 ml × 20 ml). The aqueous extract was made alkaline with aqueous ammonia and back extracted with ether (3 ml × 20 ml). The ether extract was then dried over sodium sulfate and the solvent evaporated to obtain 2.4 g (54%) of a brown oil which was purified by column chromatography and preparative TLC using chloroform:hexane, 4:1 as eluent to obtain a yellowish oil. The hydrochloride salt was prepared by bubbling HCl gas into the ethereal solution of 0.5 g of the oil and the solvent evaporated to give an off-white solid. Recrystallization from chloroform:ether gave 0.42 g (84%; net = 45%) of an off-white solid, mp 239–241 °C.

^1H NMR ($CDCl_3$): 7.3–6.9 (m, 4H, 4Ar–H); 2.2–1.25 (b, 20H, $10CH_2$); ^{13}C NMR ($CDCl_3$): 129 (s, 1C, 1CF); 123 (s, 1C, 1Ar–C); 114 (s, 2C, 2Ar–CH); 113 (d, 2C, 2Ar–CH); 61 (s, 1C, 1×4 °C); 47 (s, 2C, $2CH_2$); 34 (s, 2C, $2CH_2$); 27 (s, 2C, $2CH_2$); 26.5 (s, 1C, $1CH_2$); 25.2 (s, 1C, $1CH_2$); 22.5 (s, 2C, $2CH_2$); ^{19}F NMR ($CDCl_3$): −104 ppm; MS ESI (*m/z*, species, %): 262, $[M + H]^+$, 100; 263, $[M + 2]^+$, 20.

3.6. Preparation of 1-[1-(4-fluorophenyl)cyclohexyl]-piperidine (**4**)

A mixture of 4-bromofluorobenzene (2.0 g, 0.011 mol), magnesium turnings (1.1 g, 0.045 mol), and a few crystals of iodine in 10 ml THF were stirred vigorously under nitrogen at room temperature for 2 h. After this step, a solution of nitrile **1** (2.11 g, 0.011 mol) in 15 ml THF was added dropwise and the reaction stirred overnight. The reaction was quenched carefully with water and extracted with ether (3 ml × 20 ml). The ether extracts were combined and extracted with 2N HCl (3 ml × 20 ml). The aqueous extract was made alkaline with aqueous ammonia and back extracted with ether (3 ml × 20 ml). The ether extract was then dried over sodium sulfate and the solvent evaporated to obtain 1.6 g (56%) of a golden brown oil which was purified by column chromatography and then by preparative TLC using chloroform:hexane, 4:1 as eluent to obtain a yellowish oil. The hydrochloride salt was prepared by bubbling HCl gas into an ethereal solution of 0.25 g of the oil and the solvent evaporated. The off-white solid obtained was recrystallized in chloroform:ether to obtain 0.11 g (44%; net = 25%) of an off-white solid, mp 220–221 °C.

^1H NMR ($CDCl_3$): 7.2–6.9 (m, 4H, 4Ar–H); 2.2–1.3 (b, 20H, $10CH_2$); ^{13}C NMR ($CDCl_3$): 160 (s, 1C, 1CF); 136 (s, 1C, 1Ar–C); 129 (s, 2C, 2Ar–CH); 114 (d, 2C, 2Ar–CH); 61 (s, 1C, 1 × 4 °C); 47 (s, 2C, $2CH_2$); 34 (s, 2C, $2CH_2$); 27 (s, 2C, $2CH_2$); 26.6 (s, 1C, $1CH_2$); 25 (s, 1C, $1CH_2$); 22.6 (s, 2C, $2CH_2$); ^{19}F NMR ($CDCl_3$): −104.7 ppm; MS ESI (*m/z*, species, %): 262, $[M + H]^+$, 100; 263, $[M + 2]^+$, 22.

Anal. Calc. for $C_{17}H_{25}ClFN.0.05H_20$: C, 68.55; H, 8.46; F, 6.38; N, 4.70. Found: C, 68.35; H 8.47; F 6.36; N 4.69.

3.7. Preparation of 1-[1-(3-fluoropheny)lcyclohexyl]-pyrrolidine (**5**)

A mixture of 3-bromofluorobenzene (2.0 g, 0.011 mol), magnesium turnings (1.1 g, 0.045 mol), and a few crystals of iodine in 10 ml THF were stirred vigorously under nitrogen at room temperature for 2 h. After this step, a solution of nitrile **2** (2.0 g, 0.011 mol) in 5 ml THF was added dropwise and the reaction stirred overnight. The reaction was quenched carefully with water and extracted with ether (3 ml × 20 ml). The ether extracts were combined and extracted with 2 N HCl (3 ml × 20 ml). The aqueous extract was basified with aqueous ammonia and back extracted with ether (3 ml × 20 ml). The ether extract was then dried over

sodium sulfate and the solvent evaporated to obtain 2.36 g (87%) of a yellow-oil which was purified by column chromatography using chloroform:hexane, 4:1 as eluent. The hydrochloride salt of the yellow-oil obtained was prepared by bubbling HCl gas into an ethereal solution of 0.13 g of the oil and the solvent evaporated to give 0.097 g (75%; net = 65%) of a white solid, mp 247–249 °C.

^{1}H NMR ($CDCl_3$): 7.3–6.9 (m, 4H, 4Ar–H); 2.5–1.2 (b, 18H, $9CH_2$); ^{13}C NMR ($CDCl_3$): 161 (s, 1C, Ar–CF); 129 (s, 1C, Ar–CH); 124 (s, 1C, Ar–C); 115 (s, 1C, Ar–CH); 113 (s, 1C, Ar–CH); 60 (s, 1C, 4 °C); 45 (s, 2C, $2CH_2$); 35 (s, 2C, $2CH_2$); 25 (s, 2C, CH_2); 23 (d, 4C, $4CH_2$); ^{19}F NMR ($CDCl_3$): −104; MS ESI (*m/z*, species, %): 248, $[M + H]^+$, 100; 249, $[M + 2]^+$, 22.

Anal. Calc. for $C_{16}H_{23}ClFN.0.2H_2O$: C, 66.86; H, 8.13; F, 6.60; N, 4.87. Found: C 66.80; H 8.32; F 6.23; N 4.87.

*3.8. Preparation of 1-[1-(4-fluorophenyl)cyclohexyl]-pyrrolidine (**6**)*

A mixture of 4-bromofluorobenzene (2.0 g, 0.011 mol), magnesium turnings (1.1 g, 0.045 mol), and a few crystals of iodine in 10 ml THF were stirred vigorously under nitrogen at room temperature for 2 h. After this step, a solution of nitrile **2** (2.0 g, 0.011 mol) in 5 ml THF was added dropwise and the reaction stirred overnight. The reaction was quenched carefully with water and extracted with ether (3 ml × 20 ml). The ether extracts were combined and extracted with 2N HCl (3 ml × 20 ml). The aqueous extract was made alkaline with aqueous ammonia and back extracted with ether (3 ml × 20 ml). The ether extract was then dried over sodium sulfate and the solvent evaporated to obtain 1.2 g (44%) a yellow-oil which was purified by column chromatography and preparative TLC using chloroform:hexane, 4:1 as eluent. The hydrochloride salt of the yellow-oil obtained was prepared by bubbling HCl gas into an ethereal solution of 1.0 g of the oil and the solvent evaporated to give 0.6 g (60%; net = 26%) of a white solid, mp 223–225 °C.

^{1}H NMR ($CDCl_3$): 7.3 (m, 2H, 2Ar–H); 7.1(m, 2H, 2Ar–H); 2.6–1.1 (b, 18H, $9CH_2$); ^{13}C NMR ($CDCl_3$): 160 (s, 1C, Ar–CF); 130 (s, 1C, Ar–C); 114 (d, 4C, 4Ar–CH); 61 (s, 1C, 4 °C); 45 (s, 2C, $2CH_2$); 35 (s, 2C, $2CH_2$); 26 (s, 1C, CH_2); 23 (d, 4C, $4CH_2$) ^{19}F NMR (D_2O): −106 ppm; MS ESI (*m/z*, species, %): 248, $[M + H]^+$, 100; 249, $[M + 2]^+$, 18.

Anal. Calc. for $C_{16}H_{23}ClFN$: C, 67.71; H, 8.17; F, 6.69; N, 4.94. Found: C, 67.83; H, 8.17; F, 6.63; N, 4.76.

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