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ONE-POT SYNTHESIS OF 1-(2-, 3- OR 4-AMINOPHENYL)- AND 1-(4-AMINOBENZYL)-3,4-DIHYDROISOQUINOLINES

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Abstract – 1-Substituted 3,4-dihydro- and 1,2,3,4-tetrahydroisoquinoline derivatives were obtained in high yields from reactions of 2-(3,4-dimethoxyphenyl)ethylamine with aminobenzoic and aminophenylacetic acids in polyphosphoric acid.

INTRODUCTION

The diverse biological activities associated with the isoquinoline nucleus continue to attract a great deal of interest. Many isoquinoline derivatives are important as pharmacologically active compounds and alkaloids.[1] Recently the most often explored biological activities of the isoquinoline alkaloids are antimalarial,[2] neurotoxic,[3] antimicrobial[4], lymphocytic[5] and anticonvulsant[6] activities. Nematocidal activity[7] and cytotoxic effect on tumor cell lines have also been reported.[8]

In particular, 3,4-dihydro- or 1,2,3,4-tetrahydo-1-(2-aminophenyl)isoquinoline derivatives are useful as a new class of ligands for oligocyclic *cis*-platinum(II) antitumor complexes. *In vitro* cytotoxicity tests indicate that 1-(2-aminophenyl)isoquinolines afford the biologically most effective complexes.[9]

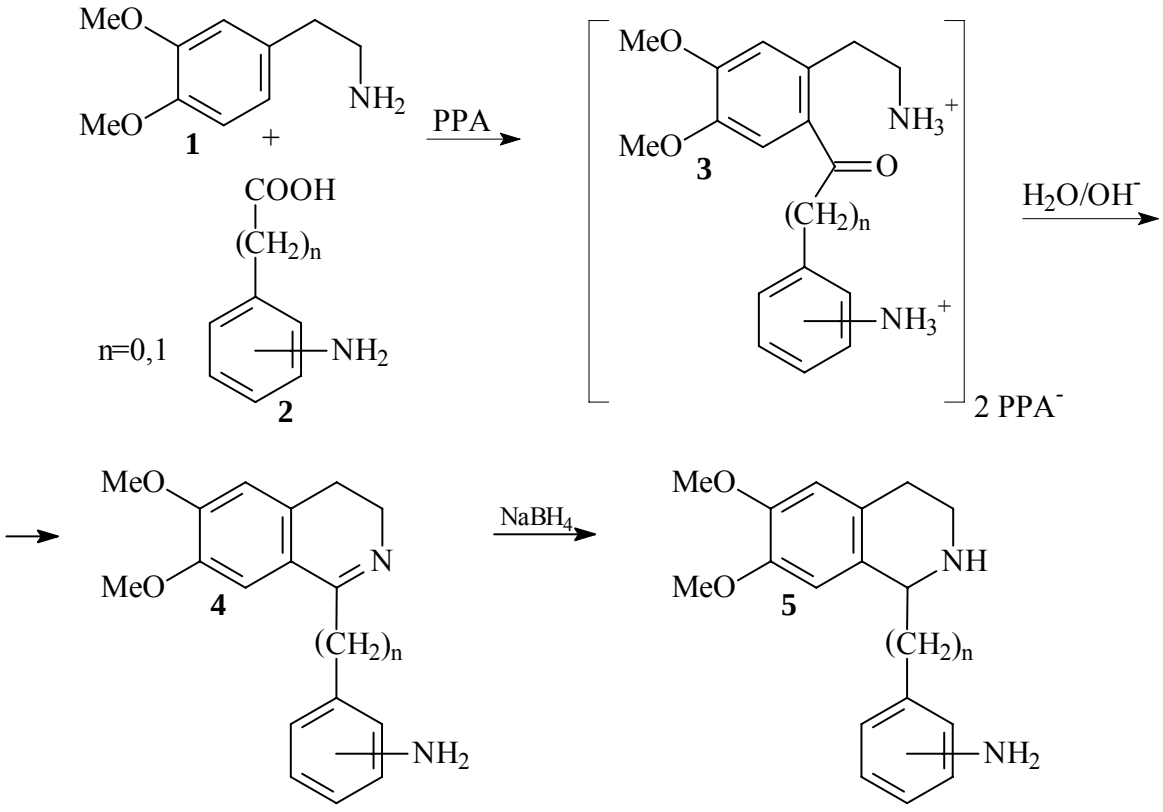
It is well known that 2-amino-3-(3-hydroxymethylisoxazol-4-yl)propionic acid (AMPA) receptor type of ionotropic glutamate receptor (iGluRs) plays a role in epileptogenesis, and several AMPA receptor antagonists have been used for prevention and treatment of epilepsy.[8] Remarkably selective and non-competitive blockade of AMPA receptor is shown by some 2,3-benzodiazepines, such as the 1-(4-aminophenyl)-4-methyl-7,8-methylendioxy-5*H*-2,3-benzodiazepine hydrochloride (GIKI 52466). Recent studies have shown that isoquinoline derivatives such as 1-(4-aminophenyl)-1,2,3,4-tetrahydroisoquinoline and 1-(3-aminophenyl)-1,2,3,4-tetrahydroisoquinoline, display anticonvulsant potencies comparable to that of GIKI 52466.[8,10]

RESULTS AND DISCUSSION

In view of the above findings, we had reasons to synthesize 1-(2-aminophenyl)-3,4-dihydroisoquinoline for our own research program. Direct synthesis of the compound from unprotected 2-aminobenzoic acid however has not been reported. Some authors have reported indirect methods for preparation of similar isoquinolines from the corresponding nitroderivatives with subsequent reduction.[10,11] Nusbaum *et al.* obtained isoquinoline derivatives by Pictet-Spengler reaction with trifluoroacetic anhydride, followed by deprotection with sodium borohydride or Bischler-Napieralski reactions followed by selective reduction of the nitro group with stannous chloride in ethyl acetate.[9]

The Friedel-Crafts acylation of activated benzene rings in the presence of polyphosphoric acid (PPA) is a very convenient method for direct synthesis of aromatic ketones.[12] Utilizing this, we have shown that the reaction of 2-(3,4-dimethoxyphenyl)ethylamine with carboxylic acids, their esters or anhydrides in PPA affords the corresponding 3,4-dihydroisoquinolines in very good yields and purity.[13] This reaction was also applied to preparation of 1-substituted 3,4-dihydro-β-carbolines.[14] In this paper we describe acylation of homoveratrylamine (**1**) with 2-aminobenzoic acid (**2**) in PPA, leading to a direct formation of 1-(2-aminophenyl)-3,4-dihydroisoquinoline, which is known to be a good ligand for *cis*-platinum(II) antitumor complexes.[8]

We found that the reaction of homoveratrylamine (**1**) with 2-aminobenzoic acid (**2**) in PPA at 80 °C for 2 h afforded the 1-substituted 3,4-dihydroisoquinoline in high yield.



Scheme 1

In this reaction acylation of the benzene ring takes place first to afford an intermediate (**3**), which spontaneously cyclizes to **4** (Scheme 1). 3-Amino- and 4-aminobenzoic acids, as well as 4-aminophenylacetic acid were also successfully used in this reaction, and the corresponding 3,4-dihydroisoquinolines were obtained in high yields (Table 1).

The 3,4-dihydroisoquinolines (**4**) obtained in this way were easily transformed to 1,2,3,4-tetrahydroisoquinolines (**5a-d**)[8,9,10] by treatment with $NaBH_4$ in methanol (Scheme 1).

Table 1

Entry	Aminocarboxylic acid (2)	Yield (%)
4a	2-NH_2-C_6H_4COOH	78
4b	3-NH_2-C_6H_4COOH	78
4c	4-NH_2-C_6H_4COOH	79
4d	4-NH_2-$C_6H_4CH_2$COOH	65
5a	2-NH_2-C_6H_4COOH	90
5b	3-NH_2-C_6H_4COOH	90
5c	4-NH_2-C_6H_4COOH	90
5d	4-NH_2-$C_6H_4CH_2$COOH	85

In conclusion, we have described a convenient one-pot method for the synthesis of 1-(2-, 3-, 4-aminophenyl and 4-aminobenzyl)-3,4-dihydro- and 1,2,3,4-tetrahydroisoquinoline derivatives, using homoveratrylamine and unprotected aminocarboxylic acids.

EXPERIMENTAL

Melting points were determined on a Boëtius hostage apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR were recorded on a Bruker DRX-250 device using $CDCl_3$ as solvent. Chemical shifts (δ, ppm) are downfield from TMS as internal standard and coupling constants are indicated in Hz. Unless otherwise noted, all the NMR spectra were taken at room temperature (*ca.* 295 K). MS spectra were recorded on a JEOL JMS-D300 spectrometer (70 eV). All new compounds had correct molecular ion peaks by mass spectrometry.

Homoveratrylamine, 2-amino-, 3-amino-, 4-aminobenzoic acids and 4-aminophenylacetic acid were purchased from Fluka. Polyphosphoric acid was obtained from 85% phosphoric acid and P_2O_5 (1:1 w/w).

Preparation of 1-substituted 3,4-dihydroisoquinolines (4a-d); Typical procedure: Homoveratrylamine (0.544 g, 3 mmol) and the corresponding aminocarboxylic acid (3.5 mmol) were dissolved in CH_2Cl_2 (3-5 mL) in an open flask and polyphosphoric acid (10 g) was added. The mixture was stirred at 80 °C for 2 h, then poured on crushed ice. The solution was carefully made basic with 25 % ammonia solution, then

extracted with CH_2Cl_2 (3 x 20 mL) and the combined extracts were dried (Na_2SO_4) and filtered through a short column with basic Al_2O_3. The products, after evaporation of the solvent, were purified by recrystallization from ether.

1-(2-Aminophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (4a): pale yellow solid, mp 128°C (lit.,[9,15] mp 129°C); ^{1}H-NMR ($CDCl_3$): 7.17 (1H, dd, *J*=6.4, 1.5 Hz, Ar), 7.15 (1H, dd, *J*=8.1, 1.5 Hz, Ar), 6.82 (1H, s, Ar), 6.75 (1H, s, Ar), 6.78-6.67 (2H, m, Ar), 5.12 (2H, br s, NH_2), 3.95 (3H, s, OCH_3), 3.81 (2H, t, C-3, *J*=7.3 Hz), 3.73 (3H, s, OCH_3), 2.70 (2H, t, C-4, *J*=7.3 Hz). ^{13}C-NMR ($CDCl_3$): 166.9, 150.78, 147.0, 146.99, 132.6, 131.0, 129.83, 121.99, 121.6, 116.8, 116.6, 111.9, 110.1, 56.1, 56.0, 47.1, 25.9. MS m/z: 282 (M^+). Anal. Calcd for $C_{17}H_{18}N_2O_2$: C 72.32, H 6.43, N 9.92. Found: C 72.46, H 6.55, N 10.05.

1-(3-Aminophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (4b): yellow solid, mp 65.5-67.5°C; ^{1}H-NMR ($CDCl_3$): 7.27-6.75 (6H, m, Ar), 3.95 (3H, s, OCH_3), 3.78 (2H, t, *J*=7.5 Hz, C-4), 3.81 (2H, br s, NH_2), 3.74 (3H, s, OCH_3), 2.71 (2H, t, C-3, *J*=7.5 Hz). ^{13}C-NMR ($CDCl_3$): 166.9, 150.9, 147.0, 146.5, 132.5, 128.8, 121.5, 119.1, 116.0, 115.3, 111.8, 110.1, 56.1, 55.9, 47.4, 25.9. MS m/z: 282 (M^+). Anal. Calcd for $C_{17}H_{18}N_2O_2$: C 72.32, H 6.43, N 9.92. Found: C 72.45, H 6.56, N 10.03.

1-(4-Aminophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (4c): yellow solid, mp 71-75°C; ^{1}H-NMR ($CDCl_3$): 7.44 (2H, d, *J*=8.6 Hz, Ar), 6.88 (1H, s, Ar), 6.77 (1H, s, Ar), 6.71 (2H, d, *J*=8.6 Hz, Ar), 4.78 (2H, br s, NH_2), 3.94 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.72 (2H, t, C-4, *J*=7.5 Hz), 2.69 (2H, t, C-3, *J*=7.5 Hz). ^{13}C-NMR ($CDCl_3$): 166.3, 150.6, 147.7, 146.8, 132.8, 130.2, 128.9, 121.6, 114.3, 111.8, 110.1, 56.0, 55.9, 47.1, 26.0. MS m/z: 282 (M^+). Anal. Calcd for $C_{17}H_{18}N_2O_2$: C 72.32, H 6.43, N 9.92. Found: C 72.47, H 6.57, N 10.04.

1-(4-Aminobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (4d): yellow solid, mp 62-65°C (**4d** hydrochloride - mp 186-187°C from MeOH, lit.,[16] mp 187-189°C); ^{1}H-NMR ($CDCl_3$): 7.85 (2H, d, *J*=8.7 Hz, Ar), 6.90 (1H, s, Ar), 6.73 (1H, s, Ar), 6.60 (2H, d, *J*=8.7 Hz, Ar), 4.42 (2H, br s, NH_2), 3.92 (3H, s, OCH_3), 3.87 (2H, s, CH_2-Bn), 3.76 (3H, s, OCH_3), 3.71 (2H, t, *J*=7.8 Hz, C-4), 2.80 (1H, t, *J*=7.7 Hz, C-3), 2.64 (1H, t, *J*=7.9 Hz, C-3). ^{13}C-NMR ($CDCl_3$): 166.0, 165.1, 152.3, 151.5, 147.5, 144.8, 132.9, 130.9, 129.3, 125.3, 119.6, 115.3, 113.6, 110.4, 110.1, 109.7, 56.0, 55.8, 47.0, 46.7, 42.3, 25.3. MS m/z: 296 (M^+). Anal. Calcd for $C_{18}H_{20}N_2O_2$: C 72.95, H 6.80, N 9.45. Found: C 73.09, H 6.93, N 9.59.

Preparation of 1-substituted 3,4-dihydroisoquinolines (5a-d); Typical procedure: To a solution of 1 mmol of the corresponding 3,4-dihydroisoquinoline **(4)** in 15 mL of methanol, $NaBH_4$ (0,04 g, 1 mmol) was added portionwise. The solution was stirred 15 min at rt, then the solvent was removed under vacuum. Water (30 mL) was added to the residue and the solution was extracted with CH_2Cl_2 (3 x 20 mL), then the combined extracts were dried (Na_2SO_4) and filtered through a short column with basic Al_2O_3. The products, after evaporation of the solvent, were purified by recrystallization from ether.

1-(2-Aminophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5a): pale yellow solid, mp 156-156.5°C (lit.,[9,11,17] mp 157°C); ^{1}H-NMR ($CDCl_3$): 7.10 (1H, dt, *J*=7.6, 0.6 Hz, Ar), 6.94 (1H, dd, *J*=7.4, 1.4 Hz), 6.71-6.62 (3H, m, Ar), 6.32 (1H, s, Ar), 5.06 (1H, s, C-1), 4.54 (2H, br s, NH_2), 3.86 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 3.22 (1H, dt, *J*=11.9, 5.2 Hz, C-3), 3.09-2.89 (2H, m, C-3 and C-4), 2.71 (1H, dt, *J*=15.7, 4.4 Hz, C-4). ^{13}C-NMR ($CDCl_3$): 147.7, 147.3, 146.2, 117.4, 116.7, 111.5, 109.95, 60.8, 55.8, 42.5, 29.2. MS m/z: 284 (M^+). Anal. Calcd for $C_{17}H_{20}N_2O_2$: C 71.81, H 7.09, N 9.85. Found: C 71.96, H 7.13, N 9.98.

1-(3-Aminophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5b): pale yellow solid, mp 121-122°C (lit.,[8] mp 121-123°C); ^{1}H-NMR ($CDCl_3$): 7.08-6.53 (5H, m, Ar), 6.30 (1H, s, Ar), 4.94 (1H, s, C-1), 3.85 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.40 (2H, br s, NH_2), 3.30-2.75 (5H, m, 2xCH_2 and NH). MS m/z: 284 (M^+). Anal. Calcd for $C_{17}H_{20}N_2O_2$: C 71.81, H 7.09, N 9.85. Found: C 71.95, H 7.14, N 9.97.

1-(4-Aminophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5c): pale yellow, mp 148-151°C (lit.,[18] mp 151-153°C); ^{1}H-NMR ($CDCl_3$): 7.02 (2H, d, *J*=8.4 Hz, Ar), 6.62 (3H, dt, *J*=7.25, 1.1 Hz, Ar), 6.27 (1H, s, Ar), 4.97 (1H, s, C-1), 3.85 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 3.50 (2H, br s, NH_2), 3.25-2.67 (5H, m, C-3, C-4 and NH). ^{13}C-NMR ($CDCl_3$): 147.4, 146.9, 145.5, 134.7, 129.7, 127.5, 114.9, 111.3, 110.9, 60.8, 55.7, 41.8, 29.2. MS m/z: 284 (M^+). Anal. Calcd for $C_{17}H_{20}N_2O_2$: C 71.81, H 7.09, N 9.85. Found: C 71.97, H 7.15, N 9.98.

1-(4-Aminobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5d): white solid, mp 142-143°C; ^{1}H-NMR ($CDCl_3$): 7.03 (2H, d, *J*=7.9 Hz, Ar), 6.67-6.58 (4H, m, Ar), 4.06 (1H, dd, *J*=4.3, 5.1 Hz, C-1), 3.84 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.50 (3H, m, NH and NH_2), 3.08 (2H, m, C-4), 2.84 (4H, m, C-3 and CH_2-Bn). ^{13}C-NMR ($CDCl_3$): 147.3, 146.8, 144.8, 130.6, 130.1, 128.6, 127.2, 115.2, 111.7, 109.4, 56.9, 55.8, 55.7, 41.7, 40.6, 29.4. MS m/z: 298 (M^+). Anal. Calcd for $C_{18}H_{22}N_2O_2$: C 72.46, H 7.43, N 9.39. Found: C 72.61, H 7.54, N 9.54.

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