DIASTEREOSELECTIVE SYNTHESIS OF *trans*-4-ARYLPIPERIDINE-3-CARBOXYLIC ACID DERIVATIVES FROM 4-ARYL-1,4-DIHYDROPYRIDINE

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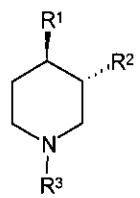
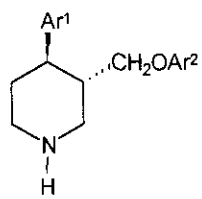
Abstract - A convenient procedure for the preparation of *trans*-3,4-disubstituted piperidines from 4-aryl-1,4-dihydropyridine is described. The diastereoselective synthesis of an unnatural amino acid, *trans*-4-arylpiperidine-3-carboxylic acid, and its derivatives is exemplified. The key steps include the construction of a *trans*-3,4-disubstituted piperidine moiety in compound (**5**), *N*-methyl carbamate of *trans*-4-aryl-piperidine-3-carboxylic acid, from 4-aryl-1,4-dihydropyridine-3-carboxylic acid methyl ester (**2**) *via* hydrogenation, reduction, and hydrolysis. Reduction of acid (**5**) with lithium aluminum hydride or with sodium borohydride provided the corresponding carbinol (**7**) or (**8**).

The piperidine ring system is present in many natural products and synthetic pharmaceutical agents.[1] For example, paroxetine and analogues are a class of 3,4-disubstituted piperidine derivatives. These compounds act in the central nervous system as potent selective serotonin (5-hydroxytryptamine) reuptake inhibitors and have been widely used as antidepressant and anti-Parkinson agents.[2,3]



R^1 = alkyl, aryl,
R^2 = CO_2R, CH_2OR, alkyl
R^3 = H, R, CO_2R



paroxetine
Ar^1 = 4-F-C_6H_4
Ar^2 = 3,4-methylenedioxyphenyl

Currently, the synthetic methods for the preparation of 3,4-disubstituted piperidine derivatives are still very limited.[1,4] In addition, these methods lack a generality for the preparation of *trans*-3,4-disubstituted piperidine derivatives since they are only used for the synthesis of some specific compounds such as amino alcohol (**8**).[3a,c] On the other hand, although the nucleophilic addition to methyl nicotinate has been known as one of the best reactions to construct a 4-substituted 1,4-dihydropyridine moiety, and this reaction has been thoroughly studied in the past decades,[4] but we found that the conversion of these unsaturated 4-substituted 1,4-dihydropyridines to the saturated *trans*-3,4-disubstituted piperidine derivatives has not been widely investigated yet. In this article, we report a convenient procedure to perform this transformation, and the diastereoselective synthesis of *trans*-3,4-disubstituted piperidine-3-carboxylic acid (**6**) as well as its derivatives from 4-substituted 1,4-dihydropyridine precursor (**2**) is exemplified.

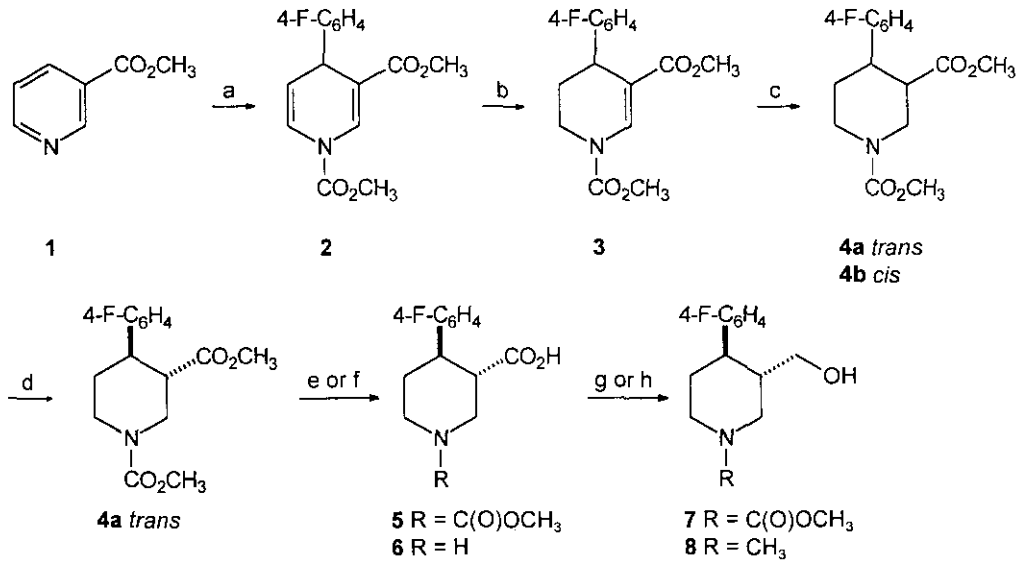
As shown in the Scheme 1, addition of 4-fluorophenylmagnesium bromide to the solution containing copper(I) chloride, 1,10-phenanthroline, and the *N*-acyl pyridium salt obtained by treatment of methyl nicotinate (**1**) with methyl chloroformate afforded the 4-aryl-1,4-dihydropyridine (**2**) in 50% yield.[3b,4] We found that the methyl chloroformate was the best acylation agent because the methyl carbamate (**2**) crystallized easier than other carbamates. We also observed that the addition of a catalytic amount (5% mol equiv.) of 1,10-phenanthroline was able to improve the yield from 40% to 50% and to decrease the amount of undesired products slightly.

Hydrogenation of dihydropyridine (**2**) under 50-60 psi of hydrogen gas in a warm solution (50 °C) of methanol and tetrahydrofuran (1:1) provided tetrahydropyridine (**3**). But the α,β-unsaturated bond in compound (**2**) was left unreacted even at longer time.[4a] Fortunately, the α,β-unsaturated bond of ester (**3**) was able to be smoothly reduced by magnesium powders in methanol. A mixture of *trans*-**4a** and *cis*-**4b** isomers of 4-arylpiperidine-3-carboxylic acid methyl ester was obtained in this reaction. However, monitoring by TLC and NMR, we found that the *cis* diastereomer can be converted to the *trans* diastereomer in a basic solution. Therefore, this mixture was treated with a 1 N potassium hydroxide methanolic solution until the *cis*-isomer (**4b**) has been transformed to the *trans*-isomer (**4a**).[5] The *trans*-piperidine ester (**4a**) was then hydrolyzed in an aqueous potassium hydroxide solution, and *N*-protected *trans*-4-arylpiperidine-3-carboxylic acid (**5**) was obtained as a colorless solid (70% yield from ester (**3**)). Acid (**5**) can either be further hydrolyzed to *trans*-4-arylnipecotic acid (**6**) in a refluxed aqueous potassium hydroxide solution, or be reduced to *N*-methylpiperidinecarbinol (**8**) with lithium aluminum hydride. Carbinol (**8**) is one of the crucial intermediates for the preparation of antidepressant paroxetine.[3c] Selective reduction of the carboxylic group in acid (**5**) to *N*-protected *trans*-piperidinecarbinol (**7**) can be achieved by reduction of the corresponding mixed anhydride of acid (**5**) with sodium borohydride.[6]

In summary, we have developed a convenient procedure for the preparation of *trans*-4-arylpiperidine-3-carboxylic acid (**5**) from unsaturated 4-aryl-1,4-dihydropyridine (**2**) *via* three steps with good yield and diastereoselectivity. Acid (**5**) can either be hydrolyzed to amino acid (**6**) or be selectively reduced to carbinol (**7**) or (**8**). Besides satisfactory yield and diastereoselectivity, this new process has the

advantages that all reagents are clean and inexpensive.

Scheme 1[a]



[a]Reagents and conditions: (a) methyl chloroformate, copper(I) chloride, 1,10-phenanthroline, 1 N 4-fluorophenylmagnesium bromide, tetrahydrofuran, 0-15 °C, 16 h, 50%; (b) hydrogen gas, 50-60 psi, 10% palladium on carbon, methanol-tetrahydrofuran (1:1), 50 °C, 24 h, 99%; (c) magnesium powder, methanol, 0 °C, 2 h, then rt, 24 h; (d) 1 N potassium hydroxide in methanol, refluxed, 30-40 min; (e) 2 N aqueous potassium hydroxide solution, methanol, rt, 16-24 h, 70% (3 steps); (f) 2 N aqueous potassium hydroxide solution, methanol, refluxed, 16-24 h, 68%; (g) triethylamine, isobutyl chloroformate, tetrahydrofuran, -50-20 °C, 2 h; then sodium borohydride, water, 0 °C, 2 h, 88%; (h) lithium aluminum hydride, tetrahydrofuran, refluxed, 72 h, 80%.

EXPERIMENTAL SECTION

1,3-Bis(methoxycarbonyl)-4-(4-fluorophenyl)-1,4-dihydropyridine (2). This reaction was performed according to the literature procedure with a little modification.[3b,4] To a solution of methyl nicotinate (5 g, 36.5 mmol) in dry tetrahydrofuran (200 mL) at rt was added dropwise methyl chloroformate (3.5 mL, 45.3 mmol). The solution was stirred at ambient temperature for 30 min, and then heated to about 50 °C for 5-10 min. To this colorless solution was added copper(I) chloride (0.18 g, 1.82 mmol) and 1,10-phenanthroline (0.33 g, 1.82 mmol). The green suspension was stirred for 20-30 min at ambient temperature, and then immersed in an ice bath. To this suspension was added dropwise 1 N solution of 4-fluorophenylmagnesium bromide in tetrahydrofuran (48 mL, 47.4 mmol). After stirring for 16 h at this temperature, the mixture was concentrated. The viscous mass was decomposed with a saturated ammonium chloride/ammonia solution (1:1), and, the water layer was extracted with ethyl acetate three times. The combined organic phase was washed with 1 N hydrochloric acid, brine,

and dried over anhydrous sodium sulfate. Evaporation of the solvent gave the crude title compound (**2**) as a yellow viscous mass. Crystallization from ethyl acetate and hexanes provided the title compound in the first crop as a colorless solid (5 g, 50%): mp 112.5-113.5 °C (lit.,[3b] 83-85 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.05 (br s, 1H), 7.40-7.05 (m, 2 H), 7.04-6.90 (m, 3 H), 5.15 (dd, J = 4.6, 8.0 Hz, 1 H), 4.45 (d, J = 4.6 Hz, 1 H), 3.92 (s, 3 H), 3.65 (s, 3 H).

1,3-Bis(methoxycarbonyl)-4-(4-fluorophenyl)-1,4,5,6-tetrahydropyridine (3). Dihydropyridine (**2**) (60 g, 206 mmol) was dissolved in a warm solution of 200 mL of methanol-tetrahydrofuran (1:1), and catalytic amount of 10% palladium on carbon (20-50 mg) was added. The mixture was put in a Parr Shaker and shaked under 50-60 psi of hydrogen gas at 50 °C overnight. After filtration of the catalyst and evaporation of the solvents, the title compound was obtained as a viscous mass (60 g, 99%). After measurement of the ^{1}H NMR spectrum, the crude compound was used directly for the next reaction without further purification: ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.34 (br s, 1H), 7.20-6.80 (m, 4 H), 4.00 (m, 1 H), 3.87 (s, 3 H), 3.66 (s, 3 H), 3.01 (td, J = 3.8, 12.8 Hz, 1 H), 2.20-1.70 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 161.5, 153.4, 139.5, 136.7, 129.0, 115.3, 109.1, 53.8, 51.5, 37.9, 35.6, 29.0. MS (EI) *m/z* 293 (M^+). HRMS calcd for $C_{15}H_{16}NO_4F$ *m/z* 293.1063 (M^+). Found: 293.1064.

***trans*-[4-(4-Fluorophenyl)-1-methoxycarbonyl]piperidine-3-carboxylic Acid (5).** To a round bottom flask equipped with a condenser containing a solution of compound (**3**) (60 g, 204 mmol) in anhydrous methanol (800 mL) in an ice bath was slowly added magnesium powder (40 g, 1.65 mol). The mixture was stirred at 0 °C for 2-4 h and then at rt overnight. After evaporation of the methanol, the mixture was carefully acidified with concentrated hydrochloric acid in an ice bath until all solids dissolved. The water layer was extracted with ethyl acetate several times. The combined organic layer was washed with brine, dried over magnesium sulfate, and concentrated to furnish mixtures (**4a**) and (**4b**) (54 g, 183 mmol) as a pale yellow viscous oil. The crude product was pure enough for hydrolysis.

To a solution containing the mixture of diastereomers (**4a**) and (**4b**) in methanol (50 mL) was added a solution of 1 N potassium hydroxide in methanol (183 mL, 183 mmol). The solution was gently refluxed for 20-30 min and then cooled to rt. After evaporation of half amount of the methanol, the solution was charged with 2 N potassium hydroxide in water (183 mL, 366 mmol). The mixture was stirred at rt overnight. After evaporation of the methanol, the mixture was acidified with 1 N hydrochloric acid to pH 1 in an ice bath. The water layer was extracted with ethyl acetate several times. The combined organic layer was washed with brine, dried over magnesium sulfate, and concentrated to give a viscous mass or a mixture of viscous oil and solid. The crude product was purified by recrystallization from ethyl acetate and hexanes to provide the title acid (**5**) as a colorless solid (40 g, 70%): mp 163.0-164.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (dd, J = 5.4, 8.6 Hz, 2 H), 6.94 (t, J = 8.6 Hz, 2 H), 4.50 (br s, 1 H), 4.25 (br s, 1 H), 3.70 (s, 3 H), 3.00-2.75 (m, 3 H), 2.60 (m, 1 H), 1.76 (m, 1 H), 1.60 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 161.7, 138.0, 128.7, 115.4, 52.9, 48.6, 46.3, 44.4, 44.3, 32.7. Anal. Calcd for $C_{14}H_{16}NO_4F$: C, 59.78; H, 5.73; N, 4.98. Found: C, 59.78; H, 5.72; N, 5.01.

***trans*-[4-(4-Fluorophenyl)piperidine]-3-carboxylic Acid Hydrochloride (6).** To a solution of crude ester (**4**) (3 g, 10.3 mmol) in methanol (3 mL) was added 1 N methanolic potassium hydroxide solution (10.8 mL, 10.8 mmol). The solution was gently refluxed for 20-30 min and then cooled to rt. After evaporation of half amount of the methanol, the mixture was charged with aqueous 2 N potassium hydroxide solution (20 mL, 40 mmol) and was refluxed for three days. The solution was cooled to rt and carefully neutralized with concentrated hydrochloric acid to pH 1. The titled amino acid hydrochloride salt was obtained and was recrystallized from methanol (1.84 g, 68%): mp 261.5-262.5 °C; ^{1}H NMR (200 MHz, CD_3OD) δ 7.22 (dd, J = 5.3, 8.8 Hz, 2 H), 6.96 (t, J = 8.8 Hz, 2 H), 3.56 (m, 1 H), 3.41 (m, 1 H), 3.25-2.90 (m, 4 H), 2.00-1.90 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 162.0, 137.6, 128.9, 114.9, 45.9, 45.3, 43.9, 42.4, 29.6. Anal. Calcd for $C_{12}H_{15}NO_2ClF$: C, 55.50; H, 5.82; N, 5.39. Found: C, 55.42; H, 5.56; N, 5.47.

***trans*-[4-(4-Fluorophenyl)-3-hydroxymethyl-1-methoxycarbonyl]piperidine (7).** To a solution of acid (**5**) (5 g, 17.8 mmol) in dry tetrahydrofuran (50 mL) at rt was added triethylamine (3.2 mL, 29.6 mmol). The solution was stirred for 20 min and then moved to a -50 °C cooling bath. To this solution was added dropwise isobutyl chloroformate (2.9 mL, 22.3 mmol). The mixture was stirred from this temperature to rt for 2 h. After filtration of the triethylamine hydrochloride and evaporation of the solvent, the viscous mass was diluted with tetrahydrofuran (30 mL). To this solution in an ice bath was added sodium borohydride (0.82 g, 21.7 mmol), followed by dropwise addition of water (10 mL). The mixture was stirred for additional 2 h after gas evolution was ceased. After evaporation of the solvent, the water layer was extracted with ethyl acetate several times. The combined organic layer was washed with brine, dried over magnesium sulfate, and concentrated to give a viscous mass. The crude product was purified by flash chromatography (20% ethyl acetate/hexanes) to furnish the title compound as a pale yellow viscous oil (4.2 g, 88%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (dd, J = 5.3, 8.6 Hz, 2 H), 6.99 (t, J = 8.6 Hz, 2 H), 4.45 (br s, 1 H), 4.25 (br s, 1 H), 3.75 (s, 3 H), 3.44 (dd, J = 3.1, 10.9 Hz, 1 H), 3.26 (dd, J = 6.6, 10.9 Hz, 1 H), 2.80 (m, 1 H), 2.76 (dd, J = 11.4, 13.3 Hz, 1 H), 2.50 (m, 1 H), 1.80-1.70 (m, 2 H), 1.60 (m, 1 H), 1.25 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5, 156.0, 139.3, 128.7, 115.4, 62.6, 52.6, 47.2, 44.4, 43.9, 43.8, 34.0. MS (EI) *m/z* 267 (M^+); HRMS calcd for $C_{14}H_{18}NO_3F$ *m/z* 267.1271 (M^+). Found: 267.1273.

***trans*-[4-(4-Fluorophenyl)-3-hydroxymethyl-1-methyl]piperidine (8).** To a suspension of lithium aluminum hydride (1.9 g, 50 mmol) in tetrahydrofuran (100 mL) in a -78 °C cooling bath was added dropwise a solution of acid (**5**) (4 g, 14.22 mmol) in tetrahydrofuran (50 mL). After completion of addition, the mixture was gently refluxed for two days. The excess lithium aluminum hydride was decomposed in an ice bath by successive dropwise addition of water (1.9 mL), 15% sodium hydroxide solution (1.9 mL), and water (5.7 mL). The precipitate was filtered and washed with ethyl acetate. The solution was concentrated and the crude product was flash chromatographed (20% ethyl acetate/hexanes) to provide the title compound as a clear viscous oil which was slowly solidified on standing (3.4 g, 100%): mp 119-120 °C (lit.,[3c] 122-126 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30-7.10 (m, 2 H), 7.05-6.90 (m, 2 H), 3.38 (dd, J = 2.9, 10.9 Hz, 1 H), 3.25-3.10 (m, 2 H), 2.93 (m, 1 H), 2.44 (br s,

1 H), 2.30 (s, 3 H), 2.25 (m, 1 H), 2.10-1.70 (m, 5 H).

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