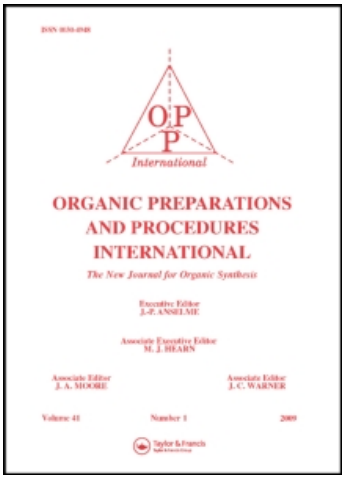

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article Zhao, Xumiao and Wan, Xiuying(1995) 'A PRACTICAL SYNTHESIS OF 4-(3',4-DIHYDROXYLPHENYL)-1,2,3,4-TETRAHYDROKOQUINOLINE', Organic Preparations and Procedures International, 27: 4, 513 — 516
To link to this Article: DOI: 10.1080/00304949509458491
URL: http://dx.doi.org/10.1080/00304949509458491

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A PRACTICAL SYNTHESIS OF 4-(3',4'-DIHYDROXYLPHENYL)-1,2,3,4-TETRAHYDROISOQUINOLINE

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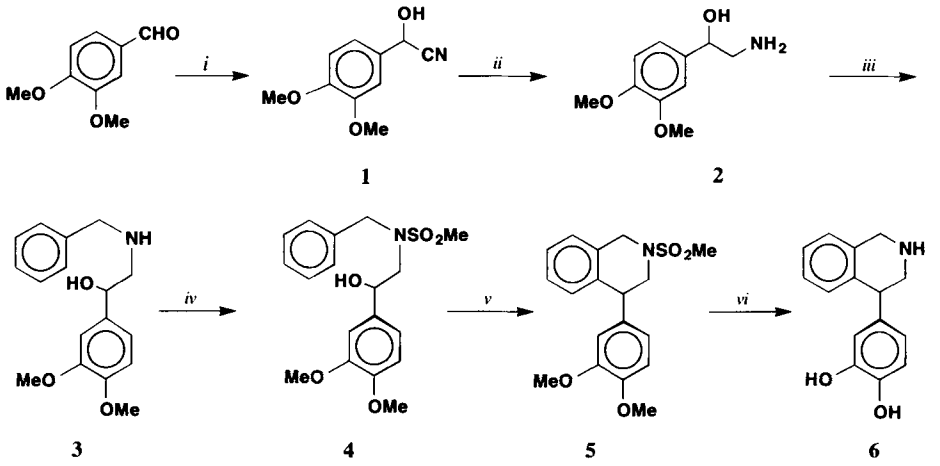
4-Aryl substituted 1,2,3,4-tetrahydroisoquinoline have been found to have dopamine agonist activity,[1] those with a 3,4-dihydroxylphenyl group at C-4 and unsubstituted on nitrogen being the most active. 4-Arylisoquinolines have been prepared by palladium-catalyzed coupling of aryl halides with diethyl (4-isoquinolyl) borane.[3] Miller and Svoboda[4] also described the coupling 4-bromoisoquinoline with either phenylboronic acid or 3,4-dimethoxylphenylboronic acid to give the 4-arylisoquinolines; however, this method suffers in that the starting materials are not readily available, thus making it impractical for large-scale synthesis. Schwan *et al.*[5] reported to use hydrobromic acid or polyphosphric acid (PPA) to prepare the 4-phenyltetrahydroisoquinoline albeit in very low yield; only cleavage products were obtained when the aromatic ring bears strong electron-withdrawing groups. Jacob and Nicoles[1, 2] used anhydrous aluminum chloride to effect the cyclization of the N-benzyl-1-(3,4-dimethoxyphenyl)-2-aminoethanol, but this method has two disadvantages. First, the yield was not very high and second, aluminum chloride is very sensitive to moisture. We now report a very efficient and economical synthesis of the most active tetrahydroisoquinoline is 4-(3',4'-dihydroxylphenyl)-1,2,3,4-tetrahydroisoquinoline (**6**)[2] on multigram scale for further biological evaluation.

In our scheme, we used sodium cyanide and ammonium chloride instead of trimethylsilyl cyanide.[2] It was reported the benzylamine and aromatic aldehyde or ketone were obtained as the major products when 48% HBr or PPA were used to cyclize N-substitutedbenzyl-1-substitutedphenyl-2- aminoethanol.[5] This indicates strong acids led not only to the dehydration of the alcohol but also to the protonation of the secondary amine. The protonated nitrogen become more electron-withdrawing

and greatly weakens the C-N bond, and consequently the C-N bond is very labile to cleavage to give the uncyclized product. On the basis of this fact, we decided to protect the secondary amine of



i) KCN, NH_4Cl, 90% *ii*) $LiAlH_4$, 79% *iii*) PhCHO, $NaBH_4$, 88%
iv) CH_3SO_2Cl, Et_3N, 96% *v*) TFA, 92% *vi*) 48% HBr, Phenol, 83%

compound **3** with the methanesulfonyl chloride, followed by trifluroacetic acid (TFA) induced cyclization of **4**, both steps proceeded in very high yield. Both the removal of methylsulfonyl group and demethylation were accomplished conveniently in the same step.

The procedure outlined here should have general application and should be very useful in the preparation the isoquinoline compounds which are highly hindered in the C-4 phenyl ring.

EXPERIMENTAL SECTION

Melting points were not corrected. Infrared spectra were recorded on a Perkin Elmer 983G IR spectrophotometer as KBr pellets. ^1H NMR spectra were recorded in ppm downfield from internal TMS on a Varian Unity instrument (200 MH_z). All solvents were distilled before use.

α-Hydroxy-3,4-dimethoxylphenylacetonitrile (1)[6].- A solution of 25 g (0.15 mol) of 3,4-dimethoxylbenzaldehyde in 120 mL of petroleum ether was shaken vigorously for 20 min with a solution of 19.6 g of (0.39 mol) of potassium cyanide and 23 g of (0.40 mol) of ammonium chloride in 90 mL of water; the flask was closed tightly during the stirring.(CAUTION: use an efficient hood). The resulting crystals were collected and washed with water and then petroleum ether. Recrystallization from benzene afforded 22.4 g (90%) of crystal needles, mp 106-107.5°. lit.[7] mp 105-107°. IR (KBr): 3360, 2900, 2315, 1610, 1590, 1420, 1390, 1300, 1240, 1040, 1020, 920, 840 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.22 (m, 1H), 6.81 (m, 2 H), 5.82 (s, 1 H), 3.85 (s, 6 H), 3.15 (broad, s, OH).

Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.73; N, 7.25. Found: C, 62.08; H, 5.64; N, 7.10

1-(3'-4'-Dimethoxyphenyl)-2-aminoethanol (2).- A solution of 12 g of (0.06 mol) of the α-hydroxyl-3,4-dimethoxylphenylacetonitrile in 200 mL of anhydrous ether was added dropwise to a

suspension of 5.5 g (0.14 mol) of lithium aluminum hydride in 340 mL of anhydrous ether and the reaction mixture stirred at reflux for 8 hrs. After cooling, 30 mL of ice-water was carefully added followed by 20-50 mL of 10% potassium hydroxide solution and then another portion of 20 mL of water. To the reaction mixture was added 400 mL methylene chloride, the white precipitate was removed by gravity filtration and thoroughly washed with another 180 mL of methylene chloride. The combined organic phase was separated from water phase and dried over sodium sulfate. Evaporation of the solvent *in vacuo* gave 10 g (84%) of product. Recrystallization from benzene-petroleum ether (5:1) yielded 9.4 g (79%) of **2** as pure colorless needles, mp 89-91°. The literature reports[2] the HCl salt melting point as 163-165°. IR (KBr): 3600, 3300, 3000, 2920, 1900, 1680, 1620, 1480, 1440, 1380, 1220, 1120, 1060, 1000, 880, 840 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.21 (m, 1 H), 6.82 (m, 2 H), 4.87 (m, 1H), 3.70 (s, 6H). 3.12 (m, 2H).

Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.66; N, 7.10. Found: C, 60.78; H, 7.46; N, 7.03

N-Methanesulfonyl-(3',4'-dimethoxylphenyl)-2-aminoethanol (4).- N-Benzyl-1-(3',4'-dimethoxyphenyl)-2-aminoethanol was prepared according to the literature procedure.[2] To 8 g (0.028 mol) of N-benzyl-1-(3',4'-dimethoxylphenyl)-2-aminoethanol in 200 mL of methylene chloride solution containing a 50 % molar excess of trimethylamine at 0° was added a 10% excess of methanesulfonyl chloride over a period of 5-15 min. Stirring at room temperature for an additional 20 min completed the reaction. The reaction mixture was added another portion 100 mL of methylene chloride. The mixture was first washed with ice water, followed by a cold 10% hydrochloric acid, saturated sodium bicarbonate solution, and brine. Drying the methylene chloride solution followed by solvent removal gave 9.7 g (96%) of **4** as a colorless oil. TLC indicate only a single product. (R_f = 0.45, 4:1 ethyl acetate-hexane). ^1H NMR ($CDCl_3$): δ 7.35 (m, 5 H), 6.7 (m, 3 H), 5.20 (q, 1 H), 4.53 (dd, 2 H), 3.88 (q, 1 H), 3. 70 (s, 6H), 3.04 (q, 1 H), 2.92 (s, 3H,).

Anal. Calcd for $C_{18}H_{23}NO_5S$: C, 59.19; H, 6.34; N 3.83. Found: C, 58.93; H, 6.24; N, 3.92

N-Methanesulfonyl-4-(3',4'-dimethoxylphenyl)-1,2,3,4-tetrahydroisoquinoline (5).- To a 50 mL of trifluoroacetic acid (TFA) was slowly added 6 g of N-benzyl-N-methanesulfonyl-1-(3',4'-dimethoxylphenyl)-2-aminoethanol; the resulting brown homogeneous solution was stirred at room temperature. After 30 min, the TFA was removed *in vacuum*. The crude product was chromatographed on silica gel over 7:2 hexane-ethyl acetate to afford 5.24 g (92%) of compound **5**, mp 137-139°. ^1H NMR ($CDCl_3$): δ 7.13 (m, 4 H), 6.85 (m, 3 H), 4.90 (q, J = 12.8 Hz, 1H), 4.70 (d, J = 15 Hz, 1H), 4.37 (d, J = 14.9 Hz, 1 H), 4.06 (dd, J = 12.9 Hz and 5.3 Hz, 1H), 3.78 (s, 3 H), 3.37 (s, 3H), 3.22 (dd, J = 12.9 and 5.2 Hz, 1 H), 2.87 (s, 3 H).

Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N, 4.03. Found: C, 62.43; H 5.87; N, 4.13

4-(3',4'-Dihydroxylphenyl)-1,2,3,4,-tetrahydroisoquinoline (6)[8].- In a 100 mL of round-bottomed flask are placed 4.6 g (132 mmol) of N-methanesulfonyl-4-(3',4'-dimethoxylphenyl)-1, 2, 3,4-tetrahydroisoquinoline, 3.6 g (3.82 mmol) of phenol and 3.94 g (23 mmol) of 48% hydrobromic acid, and 4.3 g of propionic acid. The mixture was heated to reflux for 2 hrs under argon. The resulting deeply brown colored reaction mixture is cooled to room temperature and transferred to a separatory funnel,

and washed with two 40 mL portions of ether. The aqueous phase is then added dropwise over a 30 min period to a vigorously stirred solution of 20 g of sodium hydroxide in 100 mL of water cooled by ice-water. The solution was extracted with four 50 mL of methylene chloride. The all the extracts were dried over anhydrous sodium sulfate and the solvent evaporated to afford 2.65 g (83%) of compound as a pale yellow oil (**6**). A portion of the free base upon treatment with the methanolic hydrogen chloride gave the hydrochloride, mp 219-220° after recrystallization from ethanol. The hydrobromide is also prepared by treatment of the free amine with ethereal hydrogen bromide gave the salt, mp 254-255.5° after recrystallization from ethanol; lit.[2] mp 253-255° for HBr salt. ^{1}H NMR ($CDCl_3$): δ 7.08 (m, 4 H), 6.90 (m, 1 H), 6.78 (m, 2 H), 4.75 (broad, OH), 4.68 (q, 1H), 4.10 (dd, 2 H), 3.19 (q, 1 H), 3.15 (t, 1 H), 2.84 (s, 1 H).

Anal. Calcd for $C_{15}H_{16}ClNO_2$: C, 64.86; H, 5.81; N, 5.04. Found: C, 64.74; H, 5.92; N, 5.18

Acknowledgement.- This work was supported by the National Natural Science Foundation of China and Research foundation of Zhongshan University.

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