A NOVEL SYNTHESIS OF 3-(2-AMINO-4-ETHOXYPHENYL)PYRIDINE

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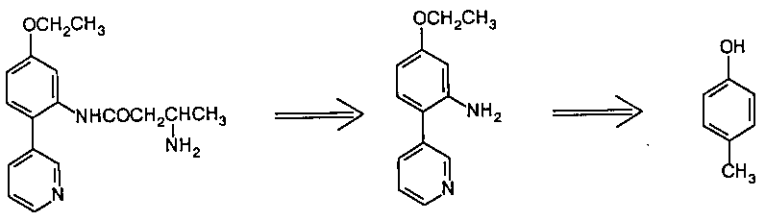
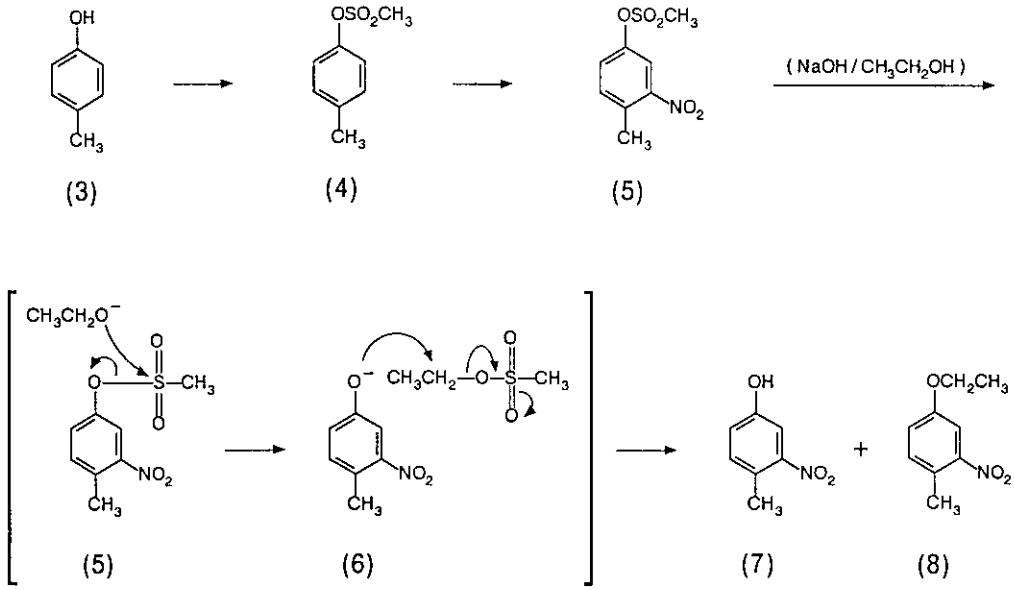
Abstract - A novel and efficient synthesis of 3-(2-amino-4-ethoxyphenyl)pyridine (*2*), a key intermediate of the antiarrhythmic agents, has been developed starting from p-cresol (*3*).

Antiarrhythmic activity has been a subject of great interest in recent years.[1] During the course of our project toward the development of novel antiarrhythmic active compounds possessing the 3-phenylpyridine framework, eg., (*1*),[2] we needed a large ammount of 3-(2-amino-4-ethoxyphenyl)pyridine (*2*) used as a key intermediate. We report herewith a novel and efficient synthesis of *2* starting from p-cresol (*3*) leading to a multi kilogram production.



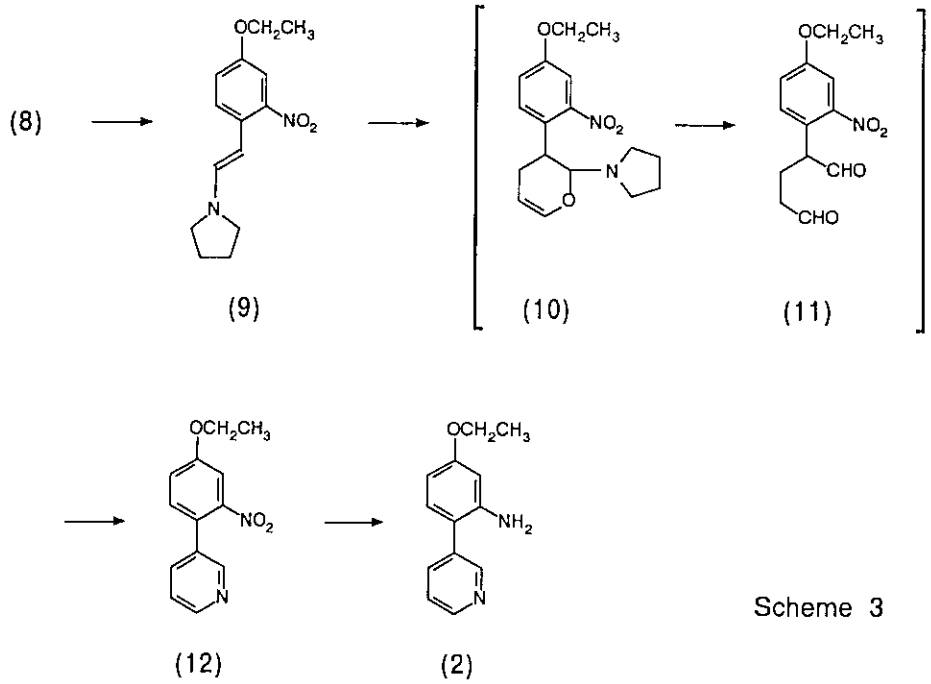
(1) (2) (3)

Scheme 1



Scheme 2

Our strategy is based on the construction of the pyridine ring from a readily accessible 1,5-dicarbonyl precursor, starting from p-cresol without employing tedious reaction conditions.[3~5] In order to activate the methyl group and to introduce the requisite amino group, p-cresol (*3*) was first converted into the mesylate (*4*) with expectation of diminishing the directing effect of the oxygen functional group. To our joy, it was found that *4* did really give the expected nitro derivative (*5*), selectively, in 73% yield upon nitration with fuming nitric acid. Having introduced the nitro group at the desired position, we next attempted to remove the methanesulfonyl group. Treatment of *5* with sodium hydroxide in aqueous ethanol furnished a 1:1 mixture of the expected phenol (*7*) and the ethyl ether (*8*) in a good yield. Since the formation of the ether (*8*) was readily interpreted by presuming the reaction between the phenoxide (*6*) and the ethyl methanesulfonate generated from *5* by ethanolysis, we treated the reaction mixture with an appropriate amount of diethyl sulfate after the hydrolysis to complete the ethylation.



Scheme 3

As expected the desired ether (*8*) could be obtained in an excellent yield directly from *5* with concomitant de-methanesulfonylation and ethylation. Although there was a precedent changing the directing effect of a phenolic oxgen in nitration by its carbonation with phosgene,[6] the present method utilizing less harmful reagent may be more practical from the synthetic point of view. Heating the o-nitrotoluene (*8*) with dimethylformamide dimethylacetal and pyrrolidine in dimethylformamide at 120°C furnished the amino-styrene (*9*) in 91% yield.[7] Hetero-Diels-Alder reaction of *9* with acrolein[8] proceeded smoothly at room temperature to give the dihydropyran (*10*), excellently, which without purification was sequentially treated with aqueous acid and hydroxylamine hydrochloride to furnish the 3-arylpyridine derivative (*12*) in 72% overall yield via the 2-arylglutalaldehyde (*11*). Although the reduction of *12* under conventional conditions using iron powder or tin salts in acidic media afforded the amine (*2*) in satisfactory yield, it was very cumbersome to remove inorganic deposits by filtration. We therefore used sodium hydrosulfide in aqueous methanol which could reduce *12* into *2* in 93% yield without accompanying any intractable by-product.

In conclusion we have developed a convenient and efficient method for the preparation of 3-(2-amino-4-ethoxyphenyl)pyridine (*2*) in a large amount. We found that methanesulfonylation of phenol was effective not only to control on the regioselective introduction of nitro group, but also on the subsequent alkylation of the oxygen functionality.

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro melting point apparatus. All melting points are uncorrected. Ir spectra were measured with a Shimadzu IR-435 instrument. ^{1}H-Nmr spectra were recorded on a JEOL JNM-GSX-270 NMR spectrometer by using Me_4Si as the internal standard. Low resolution mass spectra (ms) were obtained on a JEOL JMS-D-300.

4-Tolyl Methanesulfonate (4)

Mesyl chloride (1.87 l, 24.1 mol) was added dropwise over 40 min to a stirred solution of p-cresol (2.48 kg, 23 mol) in CH_2Cl_2 (10 l) and triethylamine (3.52 l, 25.2 mol) at 0°C. The reaction mixture was stirred at 0°C for 0.5 h and at room temperature for 2 h. The mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with 1N HCl (2 x 3 l), 1N NaOH (2 x 3 l) and sat. NaCl (2 x 4 l), and dried over Na_2SO_4, and concentrated to give 4.28 kg of crude product. The residue was recrystallized from hexane to give 3.88 kg (90.8%) of *4* as colorless crystals. mp 40°C.

^{1}H-Nmr($CDCl_3$)δ: 2.36(3H, s, Ph-C<u>H</u>$_3$), 3.11(3H, s, C<u>H</u>$_3$SO$_3$), 7.14-7.26(4H, m, Ph-<u>H</u>); ir ν(KBr) cm^{-1}: 2920, 1500, 1362, 1141, 981, 863, 838; ms (m/z) (relative intensity) 186(M^+, 42), 108(M^+-SO_2Me+H^+, 100), 107(M^+-SO_2Me, 91). <u>Anal.</u> Calcd for $C_8H_{10}O_3S$: C,51.60; H,5.41. Found: C,51.41; H,5.61.

4-Methyl-3-nitrophenyl Methanesulfonate (5)

To a cooled solution of *4* (3.72 kg, 20 mol) in concentrated sulfuric acid (98%, 20 l) was added fuming nitric acid (94%, d=1.52, 0.935 l, 21.2 mol) at 0°C at such a rate that the temperature dose not exceed 10°C with stirring. The deep red viscous reaction mixture was stirred for 3 h at room temperature and then poured onto ice. The resuting solid was collected, washed with water, dried and recrystallized from EtOH to give 3.38 kg (73%) of *5* as yellow crystals. mp 102-104°C.

^{1}H-Nmr($CDCl_3$)δ: 2.62(3H, s, Ph-C<u>H</u>$_3$), 3.22(3H, s, C<u>H</u>$_3$SO$_3$), 7.42(1H, d, J=8.79 Hz,

Ph-H_5), 7.48(1H, dd, J=8.79, 2.44 Hz, Ph-H_6), 7.92(1H, d, J=2.44 Hz, Ph-H_2); ir ν(KBr) cm^{-1}: 2951, 1524, 1365, 1189, 1162, 890, 842, 523; ms (m/z) (relative intensity) 231(M^+,16), 214(M^+-OH, 44), 149(29), 136(M^+-SO_3Me, 100), 108 (M^+-SO_2Me-NO_2, 71), 105(88). Anal. Calcd for $C_8H_9NO_5S$: C,51.46; H,3.92; N,6.06. Found: C,51.62; H,3.84; N,6.05.

4-Ethoxy-2-nitrotoluene (8)

To a stirred solution of 5 (1.05kg, 4.5 mol) in EtOH (10 l) was added 3M aq. NaOH (2.36 l). The reaction mixture was heated under reflux for 1.5 h and then Et_2SO_4 (0.3 l) and NaOH (94 g) were added to this mixture. After 1 h, a second portion of Et_2SO_4 (0.15 l) and NaOH (47 g) was added. The reaction mixture was stirred under reflux for additional 0.5 h. Until completion of reaction, as monitored by tlc, it was necessary to add an appropriate amount of Et_2SO_4 and NaOH. After reaction, the solvent was evaporated under reduced pressure and the residue was dissolved in a glycine (315 g) in water (4.7 l). This solution was heated to 60°C for 1 h to destroy excess Et_2SO_4, cooled and extracted twice with benzene (8 l, 5 l). The combined organic layers were washed with 1N NaOH (2 x 4 l), sat. NaCl (2 x 5 l), dried over Na_2SO_4 and concentrated to give a brown oil, which was distilled under reduced pressure to afford 772 g (93.8 %) of 8 as a light yellow oil; bp 140-142°C/5mmHg.

^{1}H-Nmr($CDCl_3$)δ: 1.45(3H, t, J=6.84 Hz, CH_3CH_2), 2.51(3H, s, Ph-CH_3), 4.05(2H, q, J=6.84 Hz, CH_3CH_2), 7.04(1H, dd, J=8.79, 2.44 Hz, Ph-H_5), 7.15(1H, d, J=8.79 Hz, Ph-H_6), 7.48(1H, d, J=2.44 Hz, Ph-H_3); ir ν(neat) cm^{-1}: 2973, 1624, 1526, 1345, 1243, 1042, 809; ms (m/z) (relative intensity) 181(M^+,61), 164(M^+-OH, 88), 149(69), 136(M^+-OC_2H_5, 62), 108(M^+-NO_2-C_2H_4, 100). Anal. Calcd for $C_9H_{11}NO_3$: C,59.66; H,6.12; N,7.73. Found: C,59.46; H,6.33; N,7.72.

(E)-4-Ethoxy-2-nitro-β-pyrrolidinostyrene (9)

To 8 (1.30 kg, 7.17 mol) in dry DMF (4 l) were added dimethylformamide dimethylacetal ($DMF(OMe)_2$) (1.15 l, 8.65 mol) and pyrrolidine (720 ml, 8.62 mol). The mixture was heated at 115°C for 3 h. A second portion of $DMF(OMe)_2$ (110 ml) and pyrrolidine (70 ml) was added and the mixture was heated for additional 6 h. A third portion of $DMF(OMe)_2$ (40 ml) and pyrrolidine (25 ml) was added. After completion of reaction, the volatile components were removed under reduced pressure. The residue was recrystalized from MeOH to afford 1.72kg (91.3 %) of 9 as dark violet prisms. mp 64-66°C.

^{1}H-Nmr($CDCl_3$)δ: 1.41(3H, t, J=6.83 Hz, CH_3CH_2), 1.92-1.95(4H, m, pyrrolidine

3,4-H), 3.31-3.26(4H, m, pyrrolidine 2,5-H), 4.02 (2H, q, J=6.83 Hz, $CH_3\underline{CH}_2$), 5.83(1H, d, J=13.67 Hz, CH=C<u>H</u>N), 6.97(1H, dd, J=9.03, 2.44 Hz, Ph-H_5), 7.09 (1H, d, J=13.67 Hz, C<u>H</u>=CHN), 7.37(1H, d, J=9.03 Hz, Ph-H_6), 7.38(1H, d, J=2.44 Hz, Ph-H_3); ir ν(KBr) cm^{-1}: 3419, 2959, 2845, 1596, 1549, 1503, 1052, 957, 819, 794; ms (m/z) (relative intensity) 262(M^+, 94), 164(M^+-C_2H_5-C_4H_9N, 100), 112(69). <u>Anal</u>. Calcd for $C_{14}H_{18}N_2O_3$: C,64.11; H,6.92; N,10.68. Found: C,64.09; H,6.89; N,10.76.

<u>3-(4-Ethoxy-2-nitrophenyl)pyridine (12)</u>

To a stirred solution of <u>*9*</u> (1.12 kg, 4.27 mol) in toluene (14 l) was added dropwise over 10 min acrolein (670 ml, 10.0 mol) at room temperature. After keeping overnight at room temperature with stirring, the crude dihydropyran (*10*) was obtained, which was directly used without isolation in the next reaction. The reaction mixture was cooled to 5°C with ice-water bath and was diluted with 0.25N HCl (22 l). After 0.5 h, the cooling bath was removed and the resulting mixture was allowed to warm to room temperature and stirred for 24 h. The reaction mixture was extracted with AcOEt (2 x 5 l). The combined layers were washed with sat. NaCl (2 x 4 l) and dried over Na_2SO_4, and the solvents were removed under reduced pressure to give 1.33 kg of <u>*11*</u> as a brown oil. Without purification, the material was used directly in the next reaction. The dialdehyde (*11*) was dissolved in 2-propanol (15 l). To this stirred solution a solution of hydroxylamine hydrochloride (1.22 kg, 17.6 mol) in water (6 l) was slowly added over 30 min at 0°C. The mixture was then allowed to warm to room temperature and stirred for 1 h and then heated at 100°C under reflux for 2 h. The reaction mixture was cooled to room temperature and partitioned between benzene (6 l) and 2N HCl (12 l). The organic layer was extracted with 2N HCl (2 x 3 l). The combined aqueous layers were washed with benzene (2 x 3 l), and then were made alkaline with aq. 50% NaOH and extracted with benzene (12 l, 2 x 6 l). The combined organic extracts were dried over Na_2SO_4, concentrated and chromatographed on a silica gel column using hexane-AcOEt (2:1, v/v) as eluent to give 752g (72%) of <u>*12*</u> as pale yellow crystals. mp 61-63°C.

^{1}H-Nmr($CDCl_3$)δ: 1.48(3H, t, J=6.84 Hz, $CH_2\underline{CH}_3$), 4.14(2H, q, J=6.84 Hz, $\underline{CH}_2CH_3$), 7.19(1H, dd, J=8.30, 2.44 Hz, Ph-H_5), 7.31(1H, d, J=8.30 Hz, Ph-H_6), 7.33(1H, dd, J=7.81, 4.88 Hz, Py-H_5), 7.48(1H, d, J=2.44 Hz, Ph-H_3), 7.60(1H, ddd, J=7.81, 2.44, 1.47 Hz, Py-H_4), 8.55(1H, d, J=1.47 Hz, Py-H_2), 8.63(1H, dd, J=4.88, 1.47 Hz, Py-H_6); ir ν(KBr) cm^{-1}: 3031, 1621, 1521, 1342, 1284, 1226,

1049, 869, 712; ms (m/z) (relative intensity) 245(M^++1,17), 244(M^+,100). Anal. Calcd for $C_{13}H_{12}N_2O_3$: C,63.93; H,4.95; N,11.47. Found: C,63.84; H,4.94; N,11.51.

3-(2-Amino-4-ethoxyphenyl)pyridine (2)

(Method A) To a stirred solution of *12* (110 g, 0.45 mol) in EtOH (1 l) were added stannous chloride dihydrate (344 g, 1.52 mol) and conc. HCl (0.275 l) at room temperature and then the resulting mixture was heated at 100°C under reflux for 2 h. After completion of reaction, the reaction mixture was concentrated under reduced pressure. The residue was brought to pH 12 by adding aq. 50% NaOH with stirring in ice-bath, and extracted with AcOEt (1 l, 2 x 0.5 l). The combined organic layers were washed with water (0.6 l), and sat. NaCl (2 x 0.6 l), dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on a silica gel column using $CHCl_3$ as eluent to give 67 g (69%) of *2* as pale yellow crystals. mp 121-123°C.

(Method B) To a stirred solution of *12* (800 g, 3.27 mol)in toluene (2 l) and MeOH (2 l) the solution of 70% sodium hydrosulfide (NaSH) (640 g, 8 mol) in methanol (1.4 l) and water (0.6 l) was added dropwise over 50 min at 80°C. After 15 min, 70% NaSH powder (32 g, 0.4 mol) was added to the reaction mixture and then refluxed for 30 min. After completion of reaction, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in hot water (4 l) at 50°C and $CHCl_3$ (8 l). The mixture was cooled to 0°C and aq. 10% hydrogen peroxide[9] (2.4 l) was added at such a rate that the temperature does not exceed 30°C. Stirring was continued for an additional 30 min and then the organic layer was separated. The aqueous layer was reextracted with $CHCl_3$ (4 l). The combined organic layers were washed with water (12 l), aq. 25% $NaHSO_3$ (2 x 8 l), and sat. NaCl (12 l), dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on a silica gel column using MeOH-$CHCl_3$ (3:97, v/v) as eluent to give the pure product 657g (93%) of *2* as pale yellow crystals. A sample was crystallized from hexane-Me_2CO to give colorless crystals. mp 126-128°C.

^{1}H-Nmr($CDCl_3$)δ: 1.42(3H, t, J=7.08 Hz, $CH_2\underline{CH_3}$), 3.76(2H, br s, $\underline{NH_2}$), 4.03(2H, q, J=7.08 Hz, $\underline{CH_2}CH_3$), 6.33(1H, d, J=2.44 Hz, Ph-H_3), 6.42(1H, dd, J=8.30, 2.44 Hz, Ph-H_5), 7.01(1H, d, J=8.30 Hz, Ph-H_6), 7.34 (1H, ddd, J=7.87, 4.88, 0.74 Hz, Py-H_5), 7.70(1H, ddd, J=7.87, 2.20, 1.71 Hz, Py-H_4), 8.55(1H, dd, J=4.88, 1.71 Hz, Py-H_6), 8.68(1H, dd, J=2.20, 0.74 Hz, Py-H_2); ir ν (KBr) cm^{-1}: 3383, 3306, 3302, 2990, 2907, 1604, 1465, 1256, 1187, 1054, 814, 776, 709; ms (m/z) (relative intensity) 215(M^++1,15), 214(M^+,100), 186(M^+-C_2H_4, 50), 185(M^+-C_2H_5,

73). Anal. Calcd for $C_{13}H_{14}N_2O$: C,72.87; H,6.59; N,13.07. Found: C,72.64; H,6.58; N,12.89.

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9 We found addition of a small amount of hydrogen peroxide made the isolation of the product easy.

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