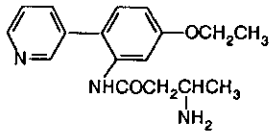
A FACILE SYNTHESIS OF 3-(2-AMINO-4-ETHOXYPHENYL)PYRIDINE

Kimiyuki Shibuya, Hiromichi Shigyo, and Tomio Ohta*

Tokyo Research Laboratories, Kowa Co., Ltd., 2-17-43,
Noguchi-cho, Higashimurayama Tokyo 189, Japan

Abstract- A facile and efficient synthesis of 3-(2-amino-4-ethoxyphenyl)pyridine (*6*), a key intermediate of the antiarrhythmic agents, has been developed starting from 3-bromopyridine (*2*) by the benzyne reaction using sodium benzylamide as the key step.

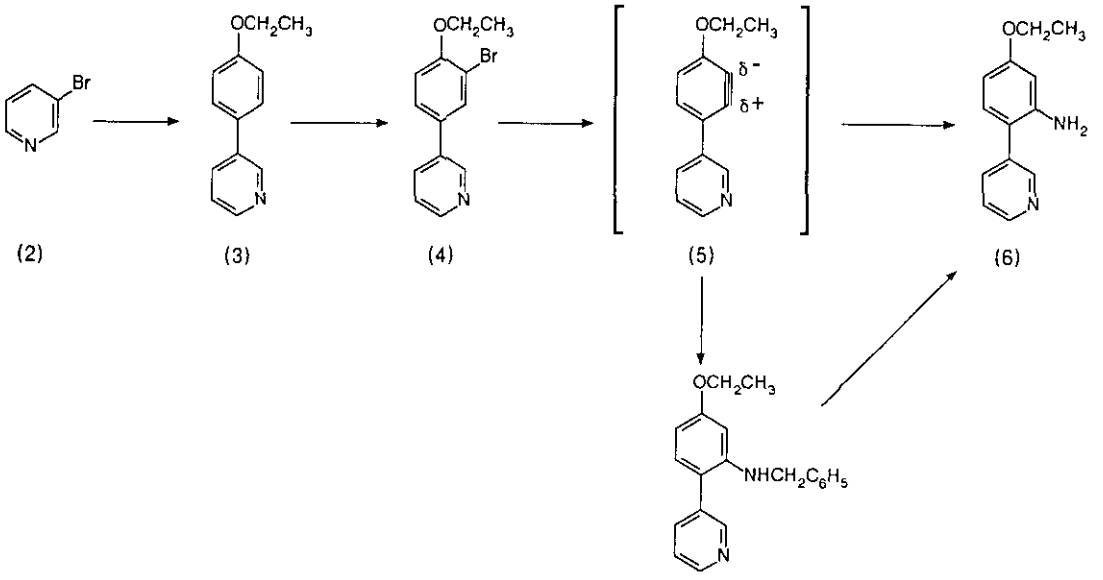
In connection with our project toward the development of novel antiarrhythmic active compounds possessing the 3-phenylpyridine framework, e.g.,(*1*),[1] we needed a substantial amount of 3-(2-amino-4-ethoxyphenyl)pyridine (*6*) used as the common key intermediate. We report here a facile and efficient synthesis of this intermediate starting from commercially available 3-bromopyridine (*2*) using nickel mediated cross-coupling reaction and benzyne reaction.



(1)

Figure 1

While conventional palladium mediated heteroarylation using diethyl(3-pyridyl)-borane [2,3] did not give fruitful result, we found that the reaction between 3-bromopyridine (*2*) and 4-ethoxyphenylmagnesium bromide in the presence of a



Scheme 1

catalytic ammount of dichlorobis(triphenylphosphine)nickel(II)[4] readily proceeded affording the desired 3-arylpyridine (*3*) in a good yield of 78.4%. Treatment of *3* with bromine in acetic acid in the presence of iron powder led to the regioselective formation of 3-(3-bromo-4-ethoxyphenyl)pyridine (*4*) in satisfactory yield. In order to introduce an amino group into the 2-position of the aryl group of *3*, we tried the reaction of *4* with sodium amide in liquid ammonia and obtained the desired amine (*6*). Thus, the reaction proceeded via the benzyne intermediate (*5*) by capturing the amide nucleophile selectively at the more electron-deficient 2-position as expected. However, the reaction was accompanied by the formation of an intractable mixture and the yield of *6* was only 17%; the Chichibabin type amination seemed to occur competitively. Subsequently, we examined the application of sodium benzylamide generated from benzylamine in tetrahydrofuran in place of the sodium amide-liquid ammonia system. Treatment of *4* with sodium benzylamine (2 equiv.) in tetrahydrofuran at 60°C readily afforded 3-(2-benzylamino-4-ethoxyphenyl)pyridine (*7*) in a good yield of 83% as a single regioisomer together with a small amount (10%) of the dehalogenation product *3*, which could be recycled. Hydrogenolytic debenzylation could be easily effected in the presence of 10% palladium on carbon to give

requisite 3-(2-amino-4-ethoxyphenyl)pyridine (*6*) in 83% yield. Although the present method involved one extra step to remove the benzyl group, it may be more practical in a large scale production since the use of liquid ammonia is avoidable and no undesirable by-products are formed in the debenzylation process.

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-FX-200 NMR spectrometer in $CDCl_3$ by using Me_4Si as the internal standard. Low resolution mass spectra (ms) were obtained on a JEOL-D-300. Reactions were carried out under nitrogen except for hydrogenation.

3-(4-Ethoxyphenyl)pyridine (3)

4-Ethoxyphenylmagnesium bromide, prepared from 4-ethoxybromobenzene (40.21 g, 200 mmol) and Mg (4.86 g, 200 mmol) in dry tetrahydrofuran (THF) (200 ml), was added dropwise over 50 min to a solution of 3-bromopyridine (23.7 g, 150 mmol) and dichlorobis(triphenylphosphine)nickel(II) (1.5 g, 2.3 mmol) in dry THF (260 ml). The reaction vessel was immersed in an ice-water bath, and the temperature was kept below 10°C during the addition. After completion of the addition, the reaction mixture was stirred at the same temperature for 1.5 h and at room temperature for 15 h. To the reaction mixture was added ammonium chloride (NH_4Cl) (2.67 g, 50 mmol) to destroy excess Grignard reagent. After 1 h, the solution was concentrated under reduced pressure and the residue was partitioned between 2N HCl (500 ml) and ethyl acetate (AcOEt) (100 ml). The aqueous layer was washed twice with AcOEt (100 ml, 50 ml). The combined organic layer was reextracted with 2N HCl (2 x 100 ml). The combined aqueous layer was washed with AcOEt (50 ml), made alkaline with solid Na_2CO_3, and extracted with AcOEt (300 ml). If necessary, the resulted deposit was filtered off through Celite. The organic layer was washed with sat. NaCl (2 x 100 ml), dried over Na_2SO_4, concentrated, and the residue was chromatographed on a silica gel column using hexane-acetone (5:3, v/v) as eluent to give 23.44 g (78.4%) of *3* as a colorless solid. A sample was recrystallized from hexane for analysis: mp 56-58°C.

^{1}H-Nmr($CDCl_3$)δ: 1.44(3H, t, J=7.08 Hz), 4.08(2H, q, J=7.08 Hz), 6.99(2H, d,

J=8.79 Hz), 7.30(1H, ddd, J=7.94, 4.82, 0.97 Hz), 7.51(2H, d, J=8.79 Hz), 7.80(1H, ddd, J=7.94, 2.44, 1.71 Hz), 8.54(1H, dd, J=4.82, 1.71 Hz), 8.82(1H, dd, J=2.44, 0.97 Hz); ir ν (KBr) cm^{-1}: 2995, 2918, 1602, 1446, 1391, 1279, 1250, 1041, 837; ms m/z (relative intensity) 200(M^++1,11), 199(M^+,71), 171(100), 149(63). Anal. Calcd for $C_{13}H_{13}NO$: C,78.36; H,6.58; N,7.03. Found: C,78.06; H,6.60; N,6.92.

3-(3-Bromo-4-ethoxyphenyl)pyridine (4)

To a stirred mixture of iron powder (0.22 g, 4 mmol), 3 (7.96 g, 40 mmol), and acetic acid (AcOH) (40 ml) was added slowly at room temperature the two thirds portion of the solution of bromine (11.2 g, 70 mmol) in AcOH (20 ml), and the mixture was stirred at 60°C for 1 h. The remaining one third portion of bromine was added and the reaction mixture was stirred at 60°C for additional 1.5 h, cooled to room temperature and diluted with water. Excess bromine was destroyed with solid $NaHSO_3$, and the mixture was made alkaline with solid Na_2CO_3 and extracted twice with benzene (150 ml, 100 ml). The combined organic layer was washed with sat. NaCl (2 x 70 ml), dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on a silica gel column using hexane- AcOEt (1:1, v/v) as eluent to give 12.24 g (88%) of 4 as a colorless solid. A sample was recrystallized from hexane-acetone for analysis: mp 95-97°C.

^{1}H-Nmr($CDCl_3$)δ: 1.50(3H, t, J=7.08 Hz), 4.16(2H, q, J=7.08 Hz), 6.98(1H, d, J=8.54 Hz), 7.34(1H, dd, J=7.94, 4.70 Hz), 7.47(1H, dd, J=8.54, 2.20 Hz), 7.77(1H, d, J=2.20 Hz), 7.80(1H, ddd, J=7.94, 2.20, 1.71 Hz), 8.57(1H, dd, J=4.70, 1.71 Hz), 8.79(1H, d, J=1.71 Hz); ir ν (KBr) cm^{-1}: 3009, 2994, 2920, 1599, 1467, 1281, 1256, 1049, 918, 817, 797, 704; ms m/z (relative intensity) 279(M^++2,61), 277(M^+,66), 251(99), 249(100). Anal. Calcd for $C_{13}H_{12}BrNO$: C,56.14; H,4.35; N,5.04. Found: C,56.23; H,4.36; N;5.06.

3-(2-Benzylamino-4-ethoxyphenyl)pyridine (7)

To a stirred mixture of benzylamine (40 ml, 360 mmol) and sodium amide (2.34 g, 60 mmol) was added at room temperature a solution of 4 (8.34 g, 30 mmol) in dry THF (25 ml). The reaction mixture was heated at 60°C for 2 h. The mixture was quenched by the portionwise addition of excess NH_4Cl (1.6 g) and methanol (20 ml). The solvent was evaporated under reduced pressure and then excess benzylamine was recovered in vacuo, (34 g, 95%). The residue was dissolved in chloroform ($CHCl_3$) (30 ml), which was extracted with 2N HCl (2 x 100 ml, 2 x 50 ml). The combined aqueous layer was washed with AcOEt (20 ml), made alkaline

with solid Na_2CO_3, and extracted with benzene (100 ml, 2 x 50 ml). The organic layer was washed with sat. NaCl (2 x 100 ml), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column using MeOH-$CHCl_3$ (3:97, v/v) as eluent to give 7.57 g (83%) of pure 7 as a brown oil, and to give a solid, 0.62 g (10%) of 3. The oily product 7 was treated with 10% hydrogen chloride EtOH solution to give a solid, which was recrystallized from EtOH-ether to give the dark green crystals, mp 173-176°C.

1H-Nmr($CDCl_3$)δ: 1.38(3H, t, J=7.08 Hz), 3.99(2H, q, J=7.08 Hz), 4.20(1H, br s,), 4.30(2H, br s,), 6.27(1H, d, J=2.44 Hz), 6.35(1H, dd, J=8.30, 2.44 Hz), 6.99(1H, d, J=8.30 Hz), 7.25-7.37(6H, m), 7.77(1H, ddd, J=7.89, 2.20, 1.71 Hz), 8.54(1H, dd, J=4.89, 1.71 Hz), 8.69(1H, dd, J=2.20, 0.97 Hz); ir ν (KBr) cm^{-1}: 3409, 3282, 3017, 1610, 1557, 1515, 1308, 1194, 1056, 784, 715; ms m/z (relative intensity) 305(M^++1,100), 304(M^+,100), 303(M^+-1,100), 251(37), 249(37), 213(63), 185(84), 149(28). Anal. Calcd for $C_{20}H_{20}N_2O$:2HCl: C,63.67; H,5.88; N,7.42. Found: C,63.83; H,5.90; N,7.34.

3-(2-Amino-4-ethoxyphenyl)pyridine (6)

(Method A) To a stirred solution of sodium amide (175 mg, 4.5 mmol) in liquid ammonia (25 ml) was added slowly finely powdered 4 (556 mg, 2 mmol). The reaction mixture soon turned yellowish-brown. After being stirred at -34°C for 8 h, to the reaction mixture was added NH_4Cl (0.15 g) to destroy excess sodium amide, followed by $CHCl_3$ (30 ml) and water (20 ml). The organic layer was washed with sat. NaCl (2 x 10 ml), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column using hexane-acetone (5:3, v/v) as eluent to afford 76 mg (17%) of 6 as yellow crystals, and 172 mg of recovered 4.

(Method B) A solution of 7 (7.5 g, 24 mmol) in AcOH (50 ml) was hydrogenated at atmospheric pressure over 1.5 g of a 10% Pd-C at 60°C for 2 h. After removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure. The residue was dissolved in water (100 ml), made alkaline with solid Na_2CO_3 and extracted twice with $CHCl_3$ (50 ml, 25 ml). The organic layer was washed with sat. NaCl (2 x 30 ml), dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on a silica gel using hexane-acetone (5:3, v/v) as eluent to afford 4.32 g (83%) of 6 as yellow crystals. A sample was recrystallized from acetone-hexane to give the colorless needles for analysis:

mp 126-128°C.

^{1}H-Nmr($CDCl_3$)δ: 1.42(3H, t, J=7.08 Hz), 3.76(2H, br s,), 4.03(2H, q, J=7.08 Hz), 6.33(1H, d, J=2.44 Hz), 6.42(1H, dd, J=8.30, 2.44 Hz), 7.01(1H, d, J=8.30 Hz), 7.34 (1H, ddd, J=7.87, 4.88, 0.74 Hz), 7.70(1H, ddd, J=7.87, 2.20, 1.71 Hz), 8.55(1H, dd, J=4.88, 1.71 Hz), 8.68(1H, dd, J=2.20, 0.74 Hz); ir ν (KBr) cm^{-1}: 3390, 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(50), 185(73), 149(32). Anal. Calcd for $C_{13}H_{14}N_2O$: C,72.87; H,6.59; N,13.07. Found: C,72.60; H,6.39; N,12.93.

ACKNOWLEDGMENTS

We thank to Dr. G. Otani, Director of Tokyo Research Laboratories, Kowa CO., Ltd., for his continuous encouragement and support.

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Received, 29th June, 1989