A Simple Highly Regioselective or Regiospecific Substitution Method of Aromatic Isoquinoline

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Abstract: A novel simple version for highly regioselective or regiospecific substitution method of aromatic isoquinoline has been developed by utilizing the reaction condition of Bischler-Napieralski cyclization. The proposed reaction mechanism was successfully indirect confirmed. In this method, chloroiminium intermedium **A** was formed from the amide compound with phosphoryl chloride, and intramolecular cyclized was preceded. The final structure of aromatic isoquinoline was obtained through removing the acidic hydrogen atom by sodium borohydride served as a base rather than reductive agent as expected.

Keywords: Regioselective substitution, regiospecific substitution, Bischler-Napieralski cyclization, aromatic isoquinoline.

INTRODUCTION

The nitrogen heterocyclic ring can be easily found in many nature compounds. The biologically active scaffold derivatives from isoquinoline [1], isoquinolone [2], benzo-isoquinoline [3], naphthoisoquinoline [4] and tetrahydro-benzyl isoquinoline [5] have been valuable subjects for many synthetic chemists (Fig. **1**).

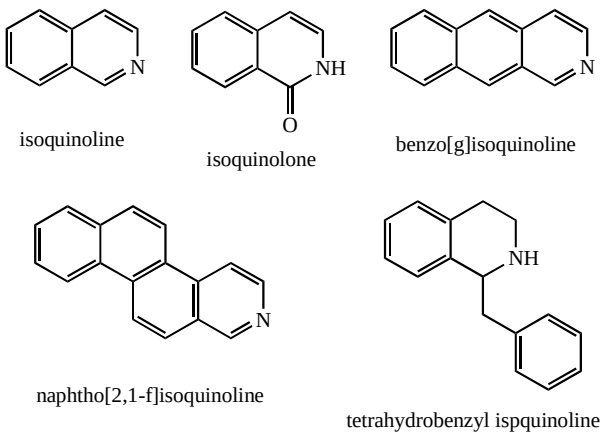


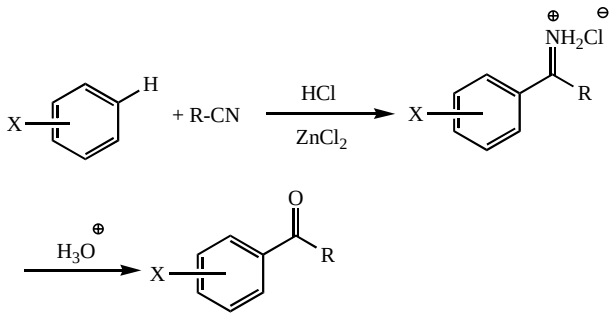
Fig. (1). The nitrogen heterocyclic ring compounds.

Miller [6] published the synthesis of isoquinolines by ozonolysis substituting indenes reductive reaction. Inter-mediate homophthalaldehydes were then treated with ammonium hydroxide to obtain aromatic isoquinolines. Previous methods, Bischler-Napieralski [7], Pictet-Spengler [8], Pomeranz-Fritsh [9], and Schlittler-Muller [10], have also been frequently employed in synthesis of isoquinoline backbone. Hibino *et al.* carried out synthesis for aromatic isoquinolines derivatives using the thermal electrocyclic reaction of 1-azahexa-1,3,5-triene system [11]. Molina's method [12] utilized a tandem electrocyclic ring closure/ Claisen rearrangement/intramolecular amination process that iminophosphorane being treated with aromatic isocyanates in toluene at high temperature leading to corresponding isoquinoline derivatives.

In this report, a simple highly regioselective or regiospecific substitutions method of aromatic isoquinoline was successfully developed through the Bischler-Napieralski cyclization reaction. Even similar reactions were studied, however, only few discussions on substitution of 2-phenethylamine affects the reactions have been revealed [13]. Moreover, taking into account that the activity of amide, or a substituted 2-phenethylamine, with various alkyl cyanide as solvent was not been investigated elsewhere.

RESULTS AND DISCUSSION

The synthesis of aromatic ketones by the electrophilic substitution reaction of benzene derivatives and nitrile group under Lewis acid based on Houben-Hoesch reaction [14] has been reported (Scheme **1**).



Scheme 1. Houben-Hoesch reaction.

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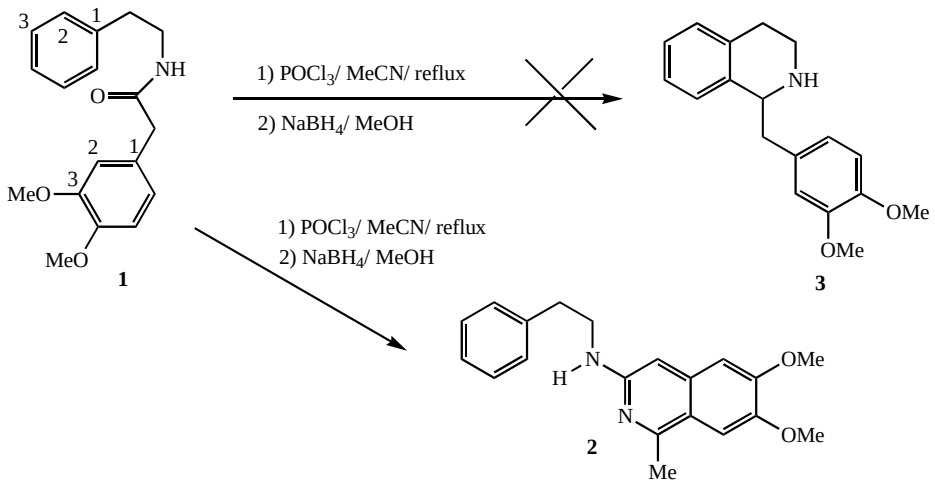
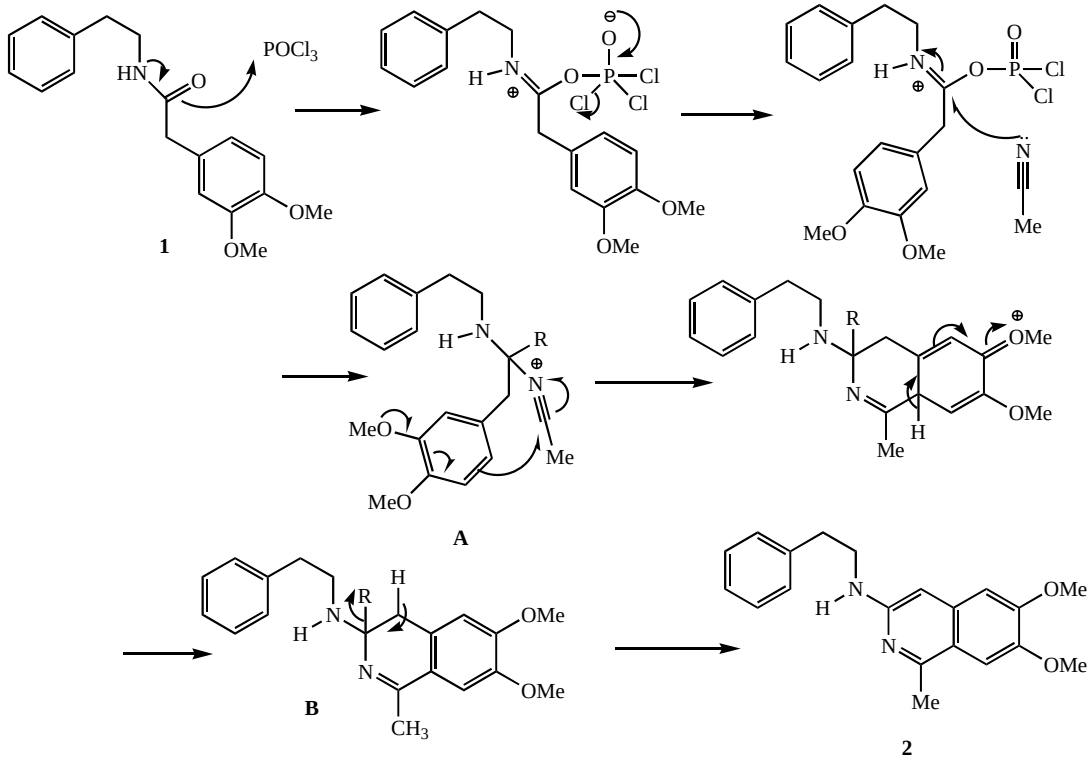


Scheme 2. Synthesis of aromatic isoquinoline by mixing amide 1 and phosphoryl chloride in dry alkyl cyanide.

According to the mechanism, synthesis of aromatic isoquinoline has been approached through the intermolecular cyclization of nitrilium salt intermediate. The amide **1** and phosphoryl chloride were mixed in dry alkylnitrile served as solvent. Interestingly, the recrystallized products from hexane/ethyl acetate were aromatic isoquinoline **2**, but not tetrahydrobenzyl isoquinoline **3** that is the expected product for Bischler-Napieralski reaction (Scheme **2**).

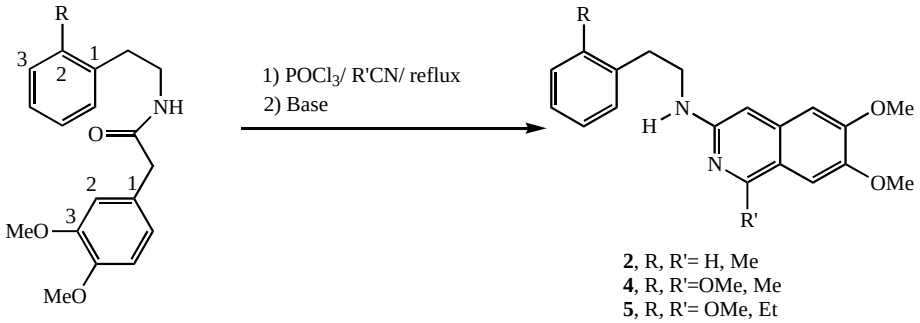
Under the condition for Bischler-Napieralski reaction, amide **1** reacted with phosphorus oxychloride to give the intermediate nitrilium salt. There was no electron donating group (e.g. methoxy group) at ortho-para position of phenethylamine. The intermediate **A** was then yielded by the Houben-Hoesch reaction. Intermediate **B** was further established through intramolecular cyclized. The structure of aromatic isoquinoline was obtained by removing the acidic hydrogen atom with base (Scheme **3**). Of particular interest was found in this particular reaction that sodium borohydride served as a base rather than reductive agent as expected. In order to confirm this special reaction, other bases were investigated, such as sodium methoxide or potassium carbonate. The results were consistent and identical results were obtained.

Based on this mechanism, preliminary studies the reaction of amide **1** against various alkyl cyanides as solvent. Compound **4** was obtained in lower yield (57%) when the



Scheme 3. Proposed mechanism for product **2**.

Table 1. Synthesis of Aromatic Isoquinolines



2, R, R'= H, Me
4, R, R'=OMe, Me
5, R, R'= OMe, Et
6, R, R'= H, Et
7, R, R'= OMe, i-Pr
8, R, R'= H, i-Pr
9, R, R'= OMe, t-Bu
10, R, R'= H, t-Bu

Compound	R	R'	Yield (%)
2	H	Me	74
4	OMe	Me	57
5	OMe	Et	27
6	H	Et	77
7	OMe	i-Pr	19
8	H	i-Pr	35
9	OMe	t-Bu	0
10	H	t-Bu	0

substituted R was methoxy group as electron donor group. Moreover, the yield of aromatic isoquinoline became lower when substituted R' of alkyl cyanide became larger. No product was obtained when the quaternary carbon structure of alkyl cyanide existed. The results were summarized in (Table **1**).

CONCLUSION

A simple yet highly regioselective or regiospecific substitutions method of aromatic isoquinoline has been successfully developed and revealed with possible reaction mechanisms. The desired products can be obtained with a simple work-up procedure with high potential to give valuable intermediates during synthesis of biologically active natural products. Other related studies have been in progress to further investigate the biological and pharmacological activity of synthesized compounds, and to extend the reactivity of the synthesis for various types of isoquinoline alkaloids.

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EXPERIMENTAL

All reactions were performed under dry nitrogen. IR spectra were measured with a Bio-Rad FTS-40 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini-200 MHz and VXR-300 MHz spectrometer using $CDCl_3$, with tetramethylsilane as the internal standard, as solvent. Low-resolution mass and high-resolution mass spectra were measured with a Hitachi M-52-Instrument or JEOL JMS-HX110 mass spectrometer. Melting points were uncorrected and were determined either using recrystallized samples or samples, which crystallized during concentration of the chromatography eluents.

N-Phenylethyl-3,4-dimethoxyphenylacetamide(1)

Thionyl chloride (7.50 mL, 102.01 mmol) was added dropwise to a solution of 3,4-dimethoxyphenylacetic acid (5.00 g, 25.45 mmol) dissolved in dichloromethane 100 mL. The mixture was refluxed for 1 h. The reaction mixture was concentrated under vacuum after cooling to rt. 20 mL water was added to the mixture and then discarded, repeated once. 2-phenylethanamine (3.34 g, 25.45 mmol) was dissolved in solution of dichloromethane 80 mL and triethyl amine 4.24 mL. Dichloromethane 15 mL was then added dropwise to this solution and stirred for 1 h at rt. The mixture was dissolved in CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. Further being dried over Na_2SO_4(s), filtered and concentrated under vacuum. The crude product was purified by recrystallization (hexane/EtOAc) to afford compound **1** (6.72 g, 88.3% yield) as a white solid. mp 105-107 ^{o}C. IR ($CHCl_3$): 3433, 1653, 1263 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ7.24-7.18(m, 3H), 7.04-7.01(m, 2H), 6.80(d, J=7.8 Hz, 1H), 6.71-6.66(m, 2H), 5.45(s, 1H), 3.88(s, 3H), 3.82(s, 3H), 3.47(s, 2H), 3.46-

3.40(m, 2H), 2.73(t, J=6.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ171.17, 149.24, 148.28, 138.60, 128.62, 128.50, 127.19, 126.39, 121.57, 112.38, 111.50, 55.90, 55.82, 43.42, 40.55, 35.38. LRMS m/z (%): 299(M^+, 10.3%), 151(M^+-$C_9H_{10}NO$, 37.1%), 91(M^+-$C_9H_{10}NO$-2xOMe, 100%).

General Procedure for Preparation of Aromatic Isoquinoline from Phenylacetamide (Table 1)

Phosphoryl chloride (132.42 mmol) was added dropwise to the solution of corresponding acetamide (22.07 mmol) dissolved in alkyl cyanide 100 mL. The mixture was refluxed in an oil bath and stirred for 4 h. The mixture was concentrated under vacuum after cooling to rt. Further dissolved in EtOAc 80 mL and washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. Samples were then dried over anhydrous Na_2SO_4(s), under reduced pressure. The mixture was dissolved in methanol 80 mL and sodium borohydride (55.18 mmol) was added slowly. The resulting mixture was stirred at rt for 12 h and concentrated under vacuum. Further being dissolved in CH_2Cl_2 and washed with saturated aqueous NH_4Cl and saturated aqueous NaCl. The mixture was dried with Na_2SO_4(s) and concentrated under vacuum. The crude product was purified by chromatography on a silica gel column.

3-(*N*-Phenylethyl)amino-6,7-dimethoxy-1-methyl-isoquinoline (2)

Yellowish solid; mp129-130 °C. IR ($CHCl_3$): 3421, 1633 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ7.33-7.28(m, 5H), 7.10(s, 1H), 6.83(s, 1H), 6.35(s, 1H), 4.50(s, 1H), 3.98(s, 3H), 3.97(s, 3H), 3.55-3.45(m, 2H), 2.98(t, J=7.2 Hz, 2H), 2.73(s, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ157.03, 149.20, 147.85, 140.05, 138.23, 128.71, 128.60, 126.62, 115.23, 103.33, 102.72, 97.17, 56.38, 56.06, 44.43, 35.14, 17.33. LRMS m/z(%): 322(M^+, 16.1%), 231(M^+-$C_6H_5CH_2$, 92.5%), 151(M^+- $C_6H_5CH_2$-2xOMe, 100%). HRMS: calcd For $C_{20}H_{22}N_2O_2$, 322.1683, found 322.1680.

3-(*N*-(2-Methoxy)phenylethyl)amino-6,7-dimethoxy-1-methylisoquinoline (4)

Yellowish solid; mp 130-132 °C. IR ($CHCl_3$): 3418, 1600 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ7.25-7.19(m, 2H), 7.09(s, 1H), 6.94-6.87(m, 2H), 6.83(s, 1H), 6.38(s, 1H), 4.64(s, 1H), 3.98(s, 3H), 3.97(s, 3H), 3.86(s, 3H), 3.45-3.40(m, 2H), 3.00(t, J=7.2 Hz, 2H), 2.73(s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ157.63, 155.23, 155.99, 152.83, 146.52, 136.18, 130.44, 127.73, 127.65, 120.55, 117.11, 110.35, 104.36, 103.83, 94.10, 55.83, 55.74, 55.24, 43.18, 30.27, 22.00. LRMS m/z (%): 352 (M^+, 10.9%), 231 (M^+-$CH_3OC_6H_5CH_2$, 100%), 91 (M^+- $C_6H_5CH_2$, 15.3%).

3-(*N*-(2-Methoxy)phenylethyl)amino-6,7-dimethoxy-1-ethylisoquinoline (5)

Yellowish solid; mp 99-101 °C. IR ($CHCl_3$): 3410, 1614 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ7.20(d, J= 7.5 Hz, 2H), 7.16(s, 1H), 6.93-6.87(m, 2H), 6.83(s, 1H), 6.37(s, 1H), 4.70-4.50(br., 1H), 3.97(s, 3H), 3.96(s, 3H), 3.86(s, 3H), 3.46(t, J=7.2 Hz, 2H), 3.08(q, J=7.8 Hz, 2H), 3.00(t, J=7.2 Hz, 2H), 1.37 (t, J=7.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ159.97, 157.67, 154.07, 152.75, 146.59, 136.59, 130.48, 127.83, 127.65, 120.56, 116.24, 110.37, 104.09, 104.2, 94.15, 55.89, 55.76, 55.26, 43.23, 30.35, 28.22, 13.41. LRMS m/z (%): 366 (M^+, 19.8%), 245 (M^+-$C_6H_5CH_2$-OMe, 100%). HRMS: calcd For $C_{22}H_{26}N_2O_3$, 366.1945, found 366.1943.

3-(*N*-Phenylethyl)amino-6,7-dimethoxy-1-ethyl-isoquinoline (6)

Yellowish solid; mp 86-87 °C. IR ($CHCl_3$): 3422, 1675 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ7.35-7.23(m, 5H), 7.16(s, 1H), 6.84(s, 1H), 6.34(s, 1H), 4.50(br., 1H), 3.97(s, 3H), 3.96(s, 3H), 3.51(d, J=7.9 Hz, 6.3Hz, 2H), 3.08(q, J=7.8 Hz, 2H), 2.98(t, J=6.9 Hz, 2H), 1. 37 (t, J=7.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ160.10, 153.81, 152.77, 146.68, 139.36, 136.49, 128.75, 128.53, 126.33, 116.36, 103.99, 94.35, 55.87, 55.77, 44.48, 35.64, 28.26, 13.43.LRMS m/z(%): 366 (M^+, 21.7%), 245 (M^+-$C_6H_5CH_2$, 100%). HRMS: calcd For $C_{21}H_{24}N_2O_2$, 366.1839, found 366.1837.

3-(*N*-(2-Methoxy)phenylethyl)amino-6,7-dimethoxy-1-isopropylisoquinoline (7)

Light brown solid; mp 65-66 °C. IR ($CHCl_3$): 3413, 1632 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ7.23-7.19 (m, 2H), 7.21 (s, 1H), 6.94-6.87(m, 2H), 6.82(s, 1H), 6.35(s, 1H), 4.80-4.40(br., 1H), 3.97(s, 3H), 3.96(s, 3H), 3.86(s, 3H), 3.60(q, J=6.6 Hz, 1H), 3.47(q, J=7.2 Hz, 2H), 3.01(t, J=7.2 Hz, 2H), 1. 37 (d, J=6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ163.12, 157.66, 154.06, 152.49, 146.45, 136.60, 130.51, 128.03, 127.61, 120.55, 115.72, 110.35, 104.06, 103.74, 94.06, 55.89, 55.75, 55.34, 43.25, 30.80, 30.44, 21.97. LRMS m/z(%): 380 (M^+, 32.7%), 259 (M^+-$C_6H_5CH_2$-OMe, 100%).HRMS: calcd For $C_{23}H_{28}N_2O_3$, 380.2101, found 380.2100.

3-(*N*-Phenylethyl)amino-6,7-dimethoxy-1-isopropyl-isoquinoline (8)

Yellowish solid; mp 95-96 °C. IR ($CHCl_3$): 3422, 1632 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ7.35-7.24(m, 6H), 6.83(s, 1H), 6.33(s, 1H), 4.80-4.60(br., 1H), 3.97(s, 6H), 3.67(q, J=6.9 Hz, 1H), 3.53(q, J=7.5 Hz, 2H), 2.99(t, J=7.5 Hz, 2H), 1. 37 (d, J=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ163.17, 153.76, 152.53, 146.59, 139.56, 136.54, 128.78, 128.49, 126.26, 115.84, 104.01, 103.64, 94.47, 55.84, 55.75, 44.48, 35.76, 30.81, 21.97. LRMS m/z (%): 350 (M^+, 26.3%), 259 (M^+-$C_6H_5CH_2$, 100%), 91 ($C_6H_5CH_2$, 48.9%). HRMS: calcd For $C_{22}H_{26}N_2O_2$, 350.2000, found 350.1996.

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