

HETEROCYCLES, Vol. 77, No. 2, 2009, pp. 1403 - 1408. © The Japan Institute of Heterocyclic Chemistry
Received, 8th September, 2008, Accepted, 15th October, 2008, Published online, 16th October, 2008
DOI: 10.3987/COM-08-S(F)110

SYNTHESIS OF 7-ANILINO-5,8-DIMETHYLISOQUINOLINES HAVING ELECTRON-ATTRACTING GROUP ON ANILINO MOIETY

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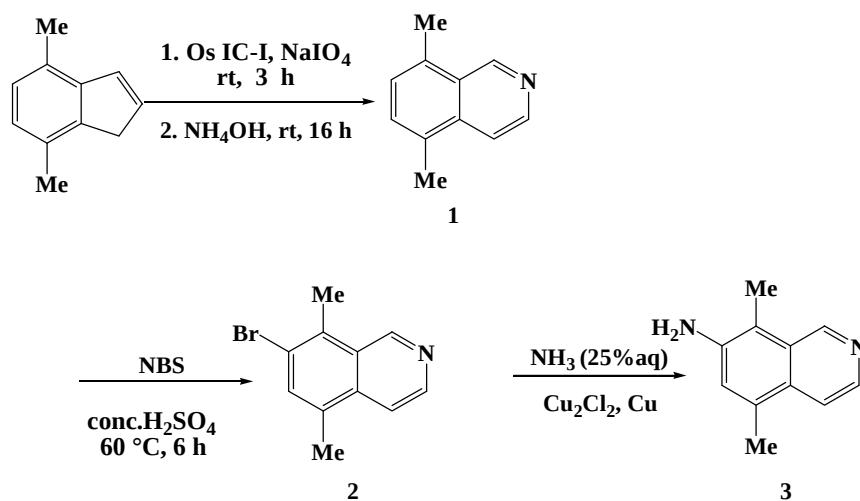
Abstract – 7-Amino-5,8-dimethylisoquinoline gave various 7-anilino-5,8-dimethylisoquinolines via a palladium-catalyzed coupling reaction with bromobenzenes having electron-attracting groups (NO₂, F).

INTRODUCTION

Isoquinoline alkaloids and variously substituted isoquinolines have been reported to have special bioactivities. For example, halide substituted isoquinoline has been reported to know an insecticide effect as to 6-bromoisquinoline¹ and carbazole derivatives containing isoquinoline ring have been reported to show anticancer and antitumor effects as to ellipticine.² Therefore, such new isoquinoline derivatives also are expected to have biological activities.

Previously, synthesis of several isoquinoline derivatives has been investigated to obtain carbazole derivatives containing isoquinoline ring.³ 5,8-Dimethylisoquinoline(**1**) is synthesized in high yield via five steps from *p*-xylene.⁴ Therefore this compound is expected as good intermediate for new isoquinoline derivatives. Recently, 7-nitro- and 6-bromo-7-nitro-5,8-dimethylisoquinolines are obtained by similar steps.⁵ In our previous work, substitution reactions of **1** was investigated and 7-bromo-5,8-dimethylisoquinoline (**2**) was selectively synthesized by the bromination of 5,8-dimethylisoquinoline (**1**) (Scheme 1). Then the substitution reactions of these isoquinolines were investigated and the catalytic amination of bromoisquinoline **2** gave 7-amino-5,8-dimethylisoquinoline (**3**) and anilinoisoquinoline derivatives having electron-donating or weak attracting groups, however, in this reaction anilinoisoquinoline derivatives having strong electron attracting groups was not obtained.⁶ In this work, 7-amino-5,8-dimethyl isoquinoline (**3**) was reacted with bromobenzenes to give new 7-anilino-5,8-dimethylisoquinolines having electron attracting groups. In this starting step, 5,8-dimethylisoquinoline (**1**) was prepared by the osmium oxidation of 4,7-dimethylindene instead of previous ozonation oxidation.

≠ Dedicate to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.



Scheme 1

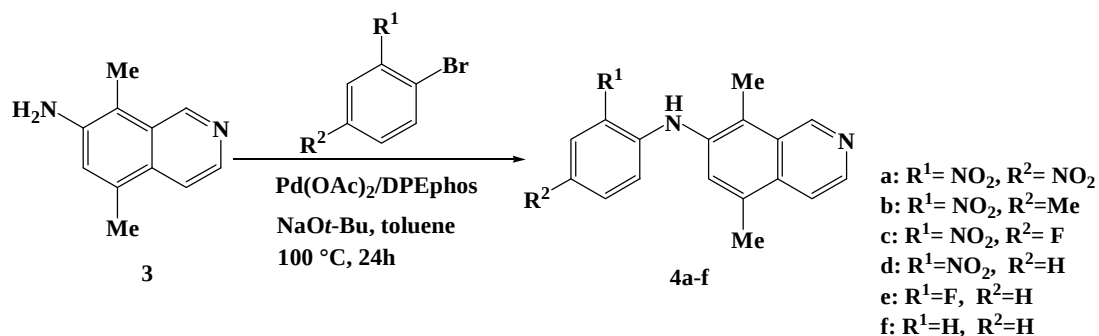
RESULTS AND DISCUSSION

Amination of 7-bromo-5,8-dimethylisoquinoline. 4,7-Dimethylindene was synthesized *via* four steps from *p*-xylene as a starting material by previous reported method.⁴ 5,8-Dimethylisoquinoline (**1**) was synthesized by the method including osmium oxidation instead of previous ozonation. The high yield was not yet obtained, but it was obtainable by more safety method than ozonation.

Bromo substituted isoquinolines (**2**) was synthesized and the catalytic amination of **2** with ammonia in the presence of copper gave 7-amino-5,8-dimethylisoquinoline(**3**) according to the previous method in Scheme 1.⁶

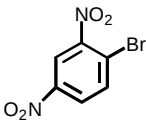
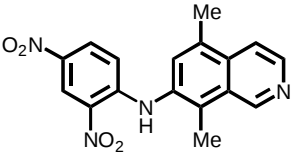
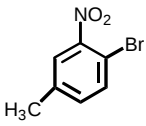
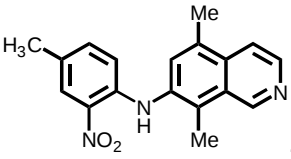
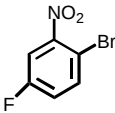
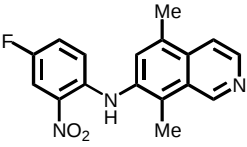
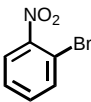
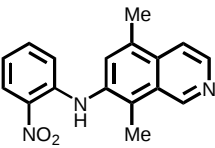
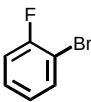
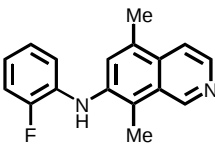
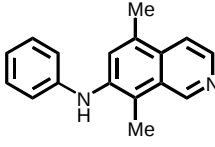
Coupling reaction of 7-amino-5,8-dimethylisoquinoline with bromobenzenes. The coupling reactions of **3** with bromobenzenes were investigated as in Scheme 2. Various 7-anilino-5,8-dimethylisoquinolines (**4a ~ f**) were synthesized by the palladium-catalyzed coupling reaction of 7-amino-5,8-dimethylisoquinoline (**3**) with bromobenzenes. The yields in the palladium-catalyzed coupling reaction are shown in Table 1.

Non-substituted bromobenzene provided 7-anilino-5,8-dimethylisoquinolines (**4f**) only in lower yield. Bromobenzenes having poor electron-attracting substituents ($R^1 = F$) on benzene ring gave 7-anilino-5,8-dimethylisoquinoline (**4e**) in low yield, but bromobenzenes having strong electron-attracting *o*-substituent ($R^1 = NO_2$) gave new 7-anilino-5,8-dimethylisoquinolines (**4a~d**) in moderate yields.



Scheme 2

Table 1 Palladium-catalyzed coupling reaction of aminoisoquinoline (3) with bromobenzenes

Bromobenzene	Product	Yield (%)	Mp (°C)
	 4a	32	181~182
	 4b	45	158~159
	 4c	37	198~199
	 4d	36	174~175
	 4e	11	153~155 (152.3~153.0) ⁶
	 4f	0.1	150~151 (152.2~153.5) ⁶

Further, bromobenzenes having another *m*-substituents ($R^2 = \text{NO}_2, \text{Me}, \text{F}$) gave 7-anilino-5,8-dimethylisoquinolines **4a~c** in similar yields. It can be considered that reaction occurs mainly by the effect of electron-attracting $R^1 = \text{NO}_2$. In the previous paper,⁶ the palladium-catalyzed coupling reaction of 7-brom-5,8-dimethylisoquinoline (**2**) with anilines on the same reaction condition is investigated and aniline give high yield of non-substituted compound **4f**, but *o*-nitroaniline is no reaction. Therefore, in this reaction, electron-attracting *o*-substituent on bromobenzene is effective, but moderate yields is considered that lower steric hindrance by the substituents has also influenced.

CONCLUSION

Various 7-anilino-5,8-dimethylisoquinolines were synthesized via a palladium-catalyzed coupling reaction of 7-amino-5,8-dimethylisoquinolines with bromobenzenes having electron-attracting groups (NO_2 , F).

EXPERIMENTAL

Instruments Melting points were determined by using a MRK MP-MG. IR spectra were recorded on a JASCO FT/IR-410 by using potassium bromide pellet or carbon tetrachloride solution. ^1H -NMR and ^{13}C -NMR spectra were acquired on a JEOL JNM-ECP500 at 500 and 125 MHz in deuteriochloroform. ^1H -NMR coupling constants are given in Hz and all chemical shifts are relative to an internal standard of tetramethylsilane. Low-resolution electron impact mass spectra were obtained on a JEOL MS station. Thin layer chromatography was performed on Merck Silica gel 60F₂₅₄.

Materials.

4,7-Dimethylindene was prepared in four steps from *p*-xylene by previous method.⁶ Osmium oxide catalyst (Wako, Os Ic-I), all solvents, and other reagents were purchased.

5,8-Dimethylisoquinoline (1) was prepared as follows: To a 100 mL, 3-necked flask was charged 4,7-dimethylindene (0.10 g, 0.69 mmol), OsO_4 (0.03 mmol), and THF- H_2O (1:1) (300 mL). The solution was stirred at rt and NaIO_4 (1.38 mmol) was added, and stirred at rt for 3 h. After filtration, 25% NH_4OH (150 mL) was added to the organic layer and stirred at rt for 16 h. When the reaction was complete, water (500 mL) was added and the solution was extracted organic layer with AcOEt. The organic layer was dried (MgSO_4), and evaporated under reduced pressure to give yellow liquid. The residual liquid was purified by distillation under reduced pressure to give 5,8-dimethylisoquinoline (**1**) as a yellow liquid (0.04 g, 39%), bp $88 \sim 94\text{ }^\circ\text{C}/1.0\text{ mmHg}$ ($107.2 \sim 109.5\text{ }^\circ\text{C}/2.5\text{ mmHg}$).⁴ ^1H -NMR (500 MHz, CDCl_3): δ 9.44 (1H, s, CH arom.), 8.58 (1H, d, CH arom., $J = 6.5\text{ Hz}$), 7.75 (1H, d, CH arom., $J = 6.5\text{ Hz}$), 7.39 (1H, d, CH arom., $J = 7.5\text{ Hz}$), 7.27 (1H, d, CH arom., $J = 7.5\text{ Hz}$), 2.75 (3H, s, CH_3), 2.62 (3H, s, CH_3); ^{13}C -NMR (125 MHz, CDCl_3): δ 149.7 (C-1), 142.8 (C-3), 135.5 (C-4a), 133.1 (C-8), 131.4 (C-6), 130.4 (C-5), 127.6 (C-7), 127.6 (C-8a), 117.3 (C-4), 18.36, 18.31 (CH_3); MS (FAB) (m/z): $157[\text{M}+1]^+$

7-Bromo-5,8-dimethylisoquinoline (2) was prepared by the bromination of **1** and the catalytic amination of **2** with ammonia in the presence of copper gave **7-amino-5,8-dimethylisoquinoline (3)** according to the previous method.⁶

Synthesis of 7-Anilino-5,8-dimethylisoquinolines

7-(2,4-Dinitroanilino)-5,8-dimethylisoquinoline (4a)

To a 100 mL, 4-necked flask equipped with a condenser, 100 mL separatory funnel and $200\text{ }^\circ\text{C}$

thermometer was charged palladium acetate (4.89 mg, 0.022 mmol) and bis[2-(diphenylphosphino)phenyl] ether (DPEphos) (17.6 mg, 0.033 mmol) under the nitrogen atmosphere. Anhydrous toluene (25 mL) was added portionwise over 5 min. After the addition, the solution was stirred for 5 min at rt under the nitrogen current. 7-Amino-5,8-dimethylisoquinoline (**3**) (75 mg, 0.436 mmol), 2,4-dinitro-1-bromobenzene (0.90 g, 0.65 mmol) and solid NaOt-Bu (0.064 g, 0.65 mmol) was added. Then, the flask was purged for 5 min with nitrogen, and the mixture was stirred at 100 °C for 24 h. When the reaction was complete, the solution was extracted organic layer with CHCl₃ and water. The organic layer was washed by aq. NaCl, dried (MgSO₄) and evaporated under reduced pressure to give yellow solid. The crude product was purified by chromatography on silica gel using AcOEt as the eluant, affording the product as a yellow solid. The solid was recrystallised from methylcyclohexane to afford a yellow crystal of 7-(2,4-dinitroanilino)-5,8-dimethylisoquinoline (**4a**) (1.71 g, 32%), mp 181~182 °C, IR (KBr, cm⁻¹) 3334, 1269 (NH), 1590, 1325 (N = O); ¹H-NMR (500 MHz, CDCl₃): δ 9.96 (1H, s, CH arom.), 9.95 (1H, s, CH arom.), 9.22 (1H, s, CH arom.), 8.71 (1H, d, CH arom., *J* = 5.7 Hz), 8.18 (1H, d, CH arom., *J* = 9.5 Hz), 7.83 (1H, d, CH arom., *J* = 5.7 Hz), 7.38 (1H, s, CH arom.), 6.77 (1H, s, NH), 2.68 (3H, s, CH₃), 2.64 (3H, s, CH₃); ¹³C-NMR (CDCl₃, 125 MHz): 149.9, 147.3, 143.9, 137.5, 135.2, 134.4, 131.0, 129.8, 129.4, 128.3, 124.1, 117.2, 116.0, 18.5, 12.7. HRMS (FAB) (*m/z*): Calcd for C₁₇H₁₄N₄O₄: 339.1094. Found M⁺: 339.1100.

7-(4-Methyl-2-nitroanilino)-5,8-dimethylisoquinoline (4b) The same palladium-catalyzed coupling above was used as for compound (**4a**), such that 45% of **4b** was isolated. mp 158~159 °C, IR (KBr, cm⁻¹): 3339, 1262, (NH), 1522, 1344 (N = O); ¹H-NMR (500 MHz, CDCl₃): δ 9.51 (1H, s, CH arom.), 9.35 (1H, s, CH arom.), 8.63 (1H, d, CH arom., *J* = 5.9 Hz), 8.05 (1H, s, CH arom.), 7.78 (1H, d, CH arom., *J* = 5.9 Hz), 7.42 (1H, s, CH arom.), 7.18 (1H, d, CH arom., *J* = 8.7 Hz), 6.68 (1H, s, NH), 2.65 (3H, s, CH₃), 2.64 (3H, s, CH₃), 2.31(3H, s, CH₃); ¹³C-NMR (CDCl₃, 125 MHz): 149.7, 143.0, 141.6, 137.3, 134.7, 134.4, 133.2, 132.7, 129.9, 128.6, 128.2, 127.2, 126.0, 117.2, 116.0, 20.1, 18.4, 12.5. HRMS (FAB) (*m/z*): Calcd for C₁₈H₁₇N₃ O₂: 308.1399. Found M⁺: 308.1398.

7-(4-Fluoro-2-nitroanilino)-5,8-dimethylisoquinoline (4c) The same palladium-catalyzed coupling above was used as for compound (**4a**), such that 37% of **4c** was isolated. mp 198~199 °C, IR (KBr, cm⁻¹) 3280, 1257 (NH), 1512, 1345 (N = O), 1258 (C-F); ¹H-NMR (500 MHz, CDCl₃): δ 9.52 (1H, s, CH arom.), 9.34 (1H, s, CH arom.), 8.65 (1H, d, CH arom., *J* = 5.5 Hz), 7.98 (1H, d, CH arom.), 7.78 (1H, d, CH arom., *J* = 6.0 Hz), 7.39 (1H, t, CH arom.), 7.15 (1H, s, CH arom.), 6.73 (1H, s, NH), 2.66 (3H × 2, s, CH₃); ¹³C-NMR (CDCl₃, 125 MHz): 149.8, 143.3, 140.7, 134.6, 134.3, 133.6, 129.8, 128.7, 124.7, 124.5, 117.4, 117.3, 117.2, 112.2, 112.0, 18.4, 12.5.

HRMS (FAB) (*m/z*): Calcd for C₁₇H₁₄FN₃ O₂: 312.1148. Found M⁺: 312.1150.

7-(2-Nitroanilino)-5,8-dimethylisoquinoline (4d) The same palladium-catalyzed coupling above was

used as for compound (**4a**), such that 52% of **4d** was isolated. mp 174~175 °C, ¹H-NMR (500 MHz, CDCl₃): δ 9.32 (1H, s, CH arom.), 8.34 (1H, d, CH arom., *J* = 5.5 Hz), 7.83 (1H, d, CH arom., *J* = 5.5 Hz), 7.53 (1H, s, CH arom.), 6.89 (2H, d, CH arom. *J* = 8.5 Hz), 6.83 (1H, t, CH arom., *J* = 8.5 Hz), 6.20 (1H, s, NH), 2.59(3H×2, s, CH₃), MS (FAB)(*m/z*) 294[M+1]⁺

7-(2-Fluoroanilino)-5,8-dimethylisoquinoline (4e) The same palladium-catalyzed coupling above was used as for compound (**4a**), such that 11% of **4e** was isolated. mp 153~155 °C (152.3~153.0),⁶ ¹H-NMR (500 MHz, CDCl₃): δ 9.39 (1H, s, CH arom.), 8.40 (1H, d, CH arom., *J* = 6.0 Hz), 7.72 (1H, d, CH arom., *J* = 6.0 Hz), 7.42 (1H, s, CH arom.), 7.16 (1H, t, CH arom., *J* = 7.5 Hz), 6.82(1H, t, CH arom., *J* = 7.5 Hz), 6.81~6.80 (2 H, m, CH arom.), 5.73 (1H, s, NH), 2.63 (3H, s, CH₃), 2.57 (3H, s, CH₃), MS (FAB)(*m/z*) 236[M+1], 238[M+3]

7-Anilino-5,8-dimethylisoquinoline (4f) The same palladium-catalyzed coupling above was used as for compound (**4a**), such that 0.1% of **4f** was isolated. mp 150~151 °C (152.3~153.0°C).⁶ ¹H-NMR (500 MHz, CDCl₃): δ 9.26 (1H, s, CH arom.), 8.74 (1H, d, CH arom., *J* = 6.0 Hz), 7.87 (1H, d, CH arom., *J* = 6.0 Hz), 7.38 (1H, s, CH arom.), 6.89 (2H, t, CH arom., *J* = 7.5 Hz), 6.80 (1H, d, CH arom., *J* = 7.5 Hz), 4.86 (1H,s, NH), 2.30 (3H×2, s, CH₃), MS (FAB)(*m/z*) 249[M+1]⁺

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