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Practical Synthesis of (6-Chloro-3-pyridyl)methylamine by Highly Selective Hydrogenation of 6-Chloro-3-pyridinecarbonitrile with Improved Raney Nickel Catalyst

Ken Tanaka,* Minoru Nagasawa,† and Hideki Sakamura†

Yokohama Research Center, Mitsubishi Chemical Corporation,
1000 Kamoshida-cho, Aoba-ku, Yokohama, Kanagawa 227-8502

†Nikko Rica Corporation, 22 Ohsanuki, Meiwa-cho, Ohra-gun, Gunma 370-0715

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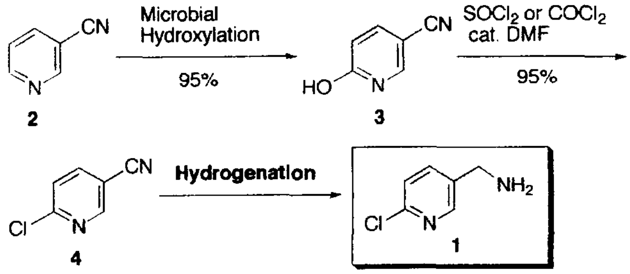
A practical synthesis of (6-chloro-3-pyridyl)methylamine (**1**), one of the key intermediates of neo-nicotinoid insecticides, by a highly selective hydrogenation of 6-chloro-3-pyridinecarbonitrile (**4**) is described. The use of an improved Raney nickel catalyst, prepared from an alloy of low nickel content (Ni 38%, Al 62%) and subjected to heat treatment in water (98 °C, 2 h) after leaching of aluminum, was highly effective for the selective hydrogenation of **4**. The hydrogenation of **4** using this catalyst was carried out in EtOH–H_2O [6 : 1 (v/v)] and NH_3 at 50 °C and 1.2—1.4 kg cm^{-2} hydrogen pressure to give **1** in 86% yield and 3-pyridylmethylamine, a dechlorinated by-product, in 2% yield.

Pyridine derivatives are important starting materials for the agrochemical industry.[1] In particular, 6-chloro-3-pyridylmethylamine (**1**) is one of the key intermediates for the manufacture of several neo-nicotinoid insecticides that show strong insecticidal activities (Scheme 1).[2] A practical synthesis of **1** is highly attractive because of its commercial importance.

Previously, Yasuda et al. reported that microbial hydroxylation of 3-pyridinecarbonitrile (**2**) gave 6-hydroxy-3-pyridinecarbonitrile (**3**) in 95% yield.[3] The resulting pyridinol **3** is easily chlorinated with $SOCl_2$[4] or $COCl_2$[5] in the presence of a catalytic amount of DMF to give 6-chloro-3-pyridinecarbonitrile (**4**) in 95% yield. These results have prompted us to develop a practical hydrogenation of **4** for the preparation of **1** (Scheme 1).

The hydrogenation of **4** has been reported by many synthetic chemists. Maurer reported that the hydrogenation of **4** with an ordinary Raney nickel catalyst in EtOH and aqueous NH_3 at room temperature and atmospheric hydrogen pressure gave **1** in moderate yield (58%) with the formation of a large amount of a secondary amine and a dechlorinated primary amine as by-products.[6] Several improved methods have been developed to decrease the generation of such by-products. Diehr reported that the hydrogenation of **4** with an anhydrous Raney cobalt catalyst in anhydrous toluene and liquid NH_3 at 100 °C and 100 kg cm^{-2} hydrogen pressure gave **1** in high yield (83%). However, it is not easy to adapt for a large scale due to the flammability of the anhydrous Raney metal catalysts, the higher cost of cobalt than that of nickel, and the employment of high hydrogen pressure.[7] Sakamoto et al. reported that the hydrogenation of **4** with a Raney nickel catalyst in anhydrous MeOH saturated with NH_3 in the presence of 2.0 molar amounts of NH_4Cl gave **1** in high yield (88%). However, the use of NH_4Cl causes complicated operations because neutralization of NH_4Cl and extraction with organic solvent can not be eliminated.[8]

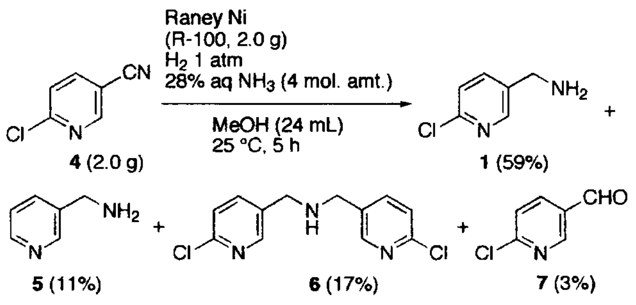


Scheme 1.

Therefore, we have improved the catalyst performance in terms of activity and selectivity by using inexpensive Raney nickel catalyst in aqueous medium without the use of additives except NH_3 at lower hydrogen pressure.[9]

Results and Discussion

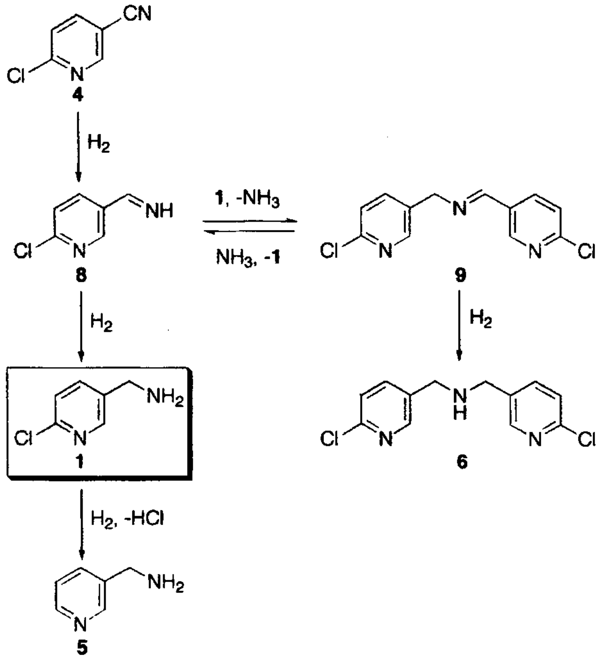
The hydrogenation of **4** was carried out using the commercially available Raney nickel catalyst, Nikko Rica R-100, in MeOH and 4.0 molar amounts of 28% aqueous NH_3 at 25 °C and atmospheric hydrogen pressure to indicate the formation of **1** in 59% yield as judged by HPLC analysis in acidic condition. However, a dechlorinated amine **5** and a secondary amine **6** were also generated in 11 and 17% yields, respectively (Eq. 1).



(1)

The possible mechanism for the formation of **1**, **5**, and **6** is shown in Scheme 2.[10] The reduction proceeds stepwise through an aldimine **8**, which is hydrogenated to **1**. The amine **1** is further dechlorinated to **5**. Some of **8** condenses with **1** to generate an aldimine **9**, which is hydrogenated to **6**. In the presence of excess NH_3, the concentration of **8** is increased by the reaction of **9** and NH_3. The analysis of the unstable intermediate **8** is important to monitor the reaction. When the reaction is analyzed by GC, **8** condenses with **1** and can be detected as **9**. On the other hand, when the reaction is analyzed by HPLC in acidic condition, **9** is hydrolyzed and can be detected as the aldehyde **7**. Therefore, the disappearance of **7** or **9**, which is confirmed through the analyses of the reaction by GC or HPLC, means that the hydrogenation of the cyano group of **4** is completed.

Optimization of Hydrogenation Conditions. To optimize the hydrogenation conditions, the effect of solvents, H_2O, and NH_3 was investigated using Nikko Rica R-100 as summarized in Table 1. The reaction was carried out for 5 h and analyzed by HPLC. When the hydrogenation was carried out under the same conditions as Eq. 1 except using EtOH instead of MeOH, the yield of **6** was decreased from 17 to 5% (Table 1, Entries 1 and 2). Under the anhydrous condition or in the presence of a large amount of H_2O, the reaction rate was decreased and the aldehyde **7** remained in 15 and 80% yield, respectively (Table 1, Entries 3 and 4). The use of 2.0 molar amounts of NH_3 increased the yield of **6** to 14% and the use of 8.0 molar amounts of NH_3 decreased the reaction rate (Table 1, Entries 5 and 6). Thus, employing 4.0 molar amounts of NH_3 and using EtOH–H_2O [6 : 1 (v/v)] as the solvent were shown to be the best reaction conditions, however, the dechlorinated amine **5** was generated in 20% yield as a by-product (Table 1, Entry 2). The separation of **5** from **1** by fractional distillation could not be accomplished on a large scale due to the thermal instability of **1**. The exothermic decomposition of the pure **1** started at 159 °C, but the decomposition of the crude **1** began even at lower temperature as judged by the DSC analyses.



Scheme 2.

Table 1. Effect of Solvent, H_2O, and NH_3 on the Hydrogenation of **4**[a)]

Entry	Solvent	H_2O	NH_3	Yield/%[b)]			
		mL	mol. amt.	**1**	**5**	**6**	**7**
1	MeOH	4.0	4.0	59	11	17	3
2	EtOH	4.0	4.0	65	20	5	<1
3	EtOH	—	4.0	62	9	5	15
4	EtOH	8.0	4.0	12	1	2	80
5	EtOH	4.0	2.0	53	13	14	10
6	EtOH	4.0	8.0	40	2	<1	50

a) Reactions were performed using **4** (2.0 g), Nikko Rica R-100 (2.0 g), and alcohols (24 mL) at 25 °C and atmospheric hydrogen pressure for 5 h. b) Determined by HPLC using biphenyl as an internal standard.

Hydrogenation with Various Raney Nickel Catalysts. As the generation of **5** was not avoided under any conditions, the hydrogenation of **4** using various Raney nickel catalysts was investigated at 25 °C and atmospheric hydrogen pressure. The preparation methods of the various Raney nickel catalysts are summarized in Table 2. As it was difficult to get fine particles of alloys of lower nickel contents (Ni < 40%), 100 mesh sieved alloy powders were used. The generation rates of **1** and **5** using the various Raney nickel catalysts are summarized in Table 3. Among the catalysts examined, the use of the improved Raney nickel catalysts, R-50 and R-41,

Table 2. Preparation Methods of Various Raney Nickel Catalysts

Raney Ni cat.	Alloy		Leaching condition[a)]	Heating condition in water
	Ni cont.	Particle size		
	%	Mesh sieved		
R-205[b)]	50	150	105 °C, 1 h	—
R-100[b)]	41	100	90 °C, 1 h	—
R-50[c)]	50	200	105 °C, 1 h	98 °C, 2 h
R-41[c)]	41	200	105 °C, 1 h	98 °C, 2 h
R-38[c)]	38	100	105 °C, 1 h	98 °C, 2 h
R-37[c)]	37	100	105 °C, 1 h	98 °C, 2 h

a) 25% aqueous NaOH was used. b) The names of the commercially available catalysts obtained from Nikko Rica Corporation. c) The names of the improved raney nickel catalysts prepared by the authors.

Table 3. Generation Rate of **1** and **5** Using Various Raney Nickel Catalysts at 25 °C and Atmospheric Hydrogen Pressure[a)]

Time	R-205[b)]			R-100[b)]			R-50[c)]			R-41[c)]		
h	**1**/%[d)]	**5**/%[d)]	**9**/%[d)]	**1**/%[d)]	**5**/%[d)]	**9**/%[d)]	**1**/%[d)]	**5**/%[d)]	**9**/%[d)]	**1**/%[d)]	**5**/%[d)]	**9**/%[d)]
4	79	9	4	69	20	2	82	6	4	72	5	17
5	76 (73[e)])	15 (10[e)])	< 1 (< 1[f)])	62 (65[e)])	28 (20[e)])	< 1 (< 1[f)])	80 (77[e)])	11 (7[e)])	< 1 (< 1[f)])	77	8	8 (8[f)])
6	—	—	—	—	—	—	—	—	—	81 (77[e)])	11 (7[e)])	< 1 (< 1[f)])

a) Reactions were performed using Raney Ni (2.0 g), **4** (2.0 g), 28% aqueous NH_3 (4.0 mol. amt.), and EtOH (24 mL) at 25 °C and atmospheric hydrogen pressure. b) The names of the commercially available Raney nickel catalysts obtained from Nikko Rica Corporation. c) The names of the improved Raney nickel catalysts prepared by the authors. d) GO area%. e) Yield determined by HPLC. f) Yield of the aldehyde **7** determined by HPLC.

prepared by heating in water (98 °C, 2 h) after leaching of aluminum,[11] showed lower generation rate of **5** than the use of the commercially available Raney nickel catalysts, R-205 and R-100. The hydrogenation using the improved Raney nickel catalysts, R-38 and R-37, prepared from alloys of lower nickel contents (Ni < 40%) by heating in water (98 °C, 2 h) after leaching of aluminum, was extremely slow at 25 °C and atmospheric hydrogen pressure. The generation rates of **1** and **5** using the improved catalysts, R-38 and R-37, was investigated at 50 °C and 1.2—1.4 kg cm^{-2} hydrogen pressure as summarized in Table 4. Less than 2.0 kg cm^{-2} hydrogen pressure was employed to carry out the hydrogenation without an autoclave. Under the same conditions, the improved catalyst, R-50, was also tested. The use of the improved catalyst, R-37, showed the lowest generation rate of **5**, but the generation rate of **1** was low. The use of the improved catalyst, R-38, showed a lower generation rate of **5** along with a higher generation rate of **1**. This reaction mixture was analyzed by HPLC to indicate the formation of **1** in 86% yield and purification by kugelrohr distillation gave **1** in 73% isolated yield with 96.0% purity. On the other hand, the use of the improved catalyst, R-50, showed higher generation rate of **5**, which required the strict control of the reaction time.

Characterization of Various Raney Nickel Catalysts. The characterizations of the various Raney nickel catalysts are summarized in Table 5. The improved Raney nickel catalysts, which showed high selectivities between hydrogenation of the cyano group of **4** and dechlorination of **1**, showed (1) lower aluminum contents, (2) larger crystallite dimensions, and (3) lower BET surface areas. These three physical properties of the Raney nickel catalysts are correlated with each other. It is well known that alloys of low nickel contents are treated with aqueous NaOH at high temperature to give the Raney nickel catalysts of low aluminum contents.[12] In the catalysts of low aluminum contents, the crystallization of the nickel crystallites can easily be proceeded by heat treatment in water to result in enlargement of their sizes. The enlargement of the crystallite sizes decreased the BET (Brunauer–Emmett–Teller) surface areas[13] of the catalysts. The physical properties of the improved Raney nickel catalyst, R-38, [aluminum contents (3.3%),

Table 5. Characterization of Various Raney Nickel Catalysts

Raney Ni cat.	Al cont. %	Crystallite dimension/Å	BET area m^2 g^{-1}-Ni
R-205[a)]	5.6	50	90
R-100[a)]	6.9	50	100
R-50[b)]	6.3	69	63
R-41[b)]	4.6	88	55
R-38[b)]	3.3	102	46
R-37[b)]	3.3	111	40

a) The names of the commercially available Raney nickel catalysts obtained from Nikko Rica Corporation. b) The names of the improved Raney nickel catalysts prepared by the authors.

Table 4. Generation Rate of **1** and **5** Using Various Raney Nickel Catalysts at 50 °C and 1.2—1.4 kg cm^{-2} Hydrogen Pressure[a)]

Time	R-50[b)]			R-38[b)]			R-37[b)]		
h	**1**/%[c)]	**5**/%[c)]	**9**/%[c)]	**1**/%[c)]	**5**/%[c)]	**9**/%[c)]	**1**/%[c)]	**5**/%[c)]	**9**/%[c)]
3	83	12	1	—	—	—	—	—	—
4	78	17	< 1	58	< 1	33	—	—	—
5	73 (73[d)])	23 (15[d)])	< 1 (< 1[e)])	76	1	16	—	—	—
6				88	2	5	55	< 1	32
7				90	2	1	—	—	—
8				91	2	< 1	76	1	11
9				91 (86[d)])	3 (2[d)])	< 1 (< 1[e)])	82	2	8
10							84	2	6
11							87 (77[d)])	2 (2[d)])	3 (3[e)])

a) Reactions were performed using Raney Ni (4.5 g), **4** (30 g), 28% aqueous NH_3 (4.0 mol. amt.), and EtOH 257 mL) at 50 °C and 1.2—1.4 kg cm^{-2} hydrogen pressure. b) The names of the improved Raney nickel catalysts prepared by the authors. c) GC area %. d) Yield determined by HPLC. e) Yield of the aldehyde **7** determined by HPLC.

nickel crystallite dimension (102 Å), BET surface area (46 $m^2\,g^{-1}$-Ni)] were shown to be the best for the selective hydrogenation of **4** at less than 2.0 $kg\,cm^{-2}$ hydrogen pressure.

In conclusion, the use of the improved Raney nickel catalyst, R-38, prepared from an alloy of low nickel content (Ni 38%, Al 62%) and subjected to heat treatment in water (98 °C, 2 h) after leaching of aluminum, is highly effective for the selective hydrogenation of 6-chloro-3-pyridinecarbonitrile (**4**). In this hydrogenation, the desired amine **1** was obtained in high yield and the generation of a dechlorinated amine **5** could be minimized. This method has a number of practical advantages: (1) no need of an expensive high-pressure autoclave, additives except NH_3, and strict safety controls; (2) the employment of low temperature, low hydrogen pressure, and aqueous medium; (3) the easy control of the reaction time. This procedure was successfully applied to a multi-hundred kilogram scale synthesis of **1**.

Experimental

General. Melting points were uncorrected. ^1H and ^{13}C NMR spectra were collected at 300 MHz. Yields and purities were determined by HPLC (column: MCI-GEL ODS, column temp: 40 °C, eluent: CH_3CN–H_2O (45 : 55); NaH_2PO_4 = 0.05 M; sodium lauryl sulfate = 0.05 M (1 M = 1 mol dm^{-3}); pH 4.5; 1.0 mL min^{-1}, detect: 254 nm) using biphenyl as an internal standard. Reactions were monitored by GC (column: DB-1; 0.25 mm×25 m, detector: FID, carrier gas: He). The physical properties of the catalysts were evaluated by the conventional methods.[13,14] The aluminum contents of the catalysts were examined by M/50 EDTA titration method. The dimensions of the nickel crystallites were examined by the X-ray powder diffractometry.[14] The surface areas ($m^2\,g^{-1}$-Ni) were examined by BET method.[13] All solvents and reagents were plant grade and were used without further purification. The Raney nickel catalysts R-100 and R-205 were commercially available from Nikko Rica Corporation. 6-Chloro-3-pyridinecarbonitrile (**4**) was prepared by microbial hydroxylation of 3-pyridinecarbonitrile (**2**) followed by chlorination of hydroxy group with $SOCl_2$ according to the literature.[3,4]

Isolation of Bis(6-chloro-3-pyridylmethyl)amine (6) and 6-Chloro-3-pyridinecarbaldehyde (7). A mixture of the Raney nickel catalyst (Nikko Rica R-100, 1.0 g), 6-chloro-3-pyridinecarbonitrile (**4**) (1.0 g, 7.22 mmol), MeOH (12 mL), and 28% aqueous NH_3 (2.0 mL, 28.9 mmol) was stirred at 25 °C and atmospheric hydrogen pressure for 4 h. The reaction mixture was filtered and washed with MeOH. The solvent was removed under reduced pressure and the residual oil was diluted with water (25 mL). The resulting mixture was adjusted at pH 6.5 with 1 M aqueous HCl and extracted with $CHCl_3$ (25 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure and the residual oil was purified by preparative TLC with EtOAc to give **7** (15.4 mg, 0.108 mmol, R_f = 0.8) and **6** (37.7 mg, 0.141 mmol, R_f = 0.5).

6-Chloro-3-pyridinecarbaldehyde (7).[15] Colorless crystals; mp 70—71 °C; IR (KBr) 1712 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ = 7.52 (1H, ddd, J = 0.6, 2.4, 8.1 Hz), 8.14 (1H, dd, J = 2.4, 8.1 Hz), 8.87 (1H, dd, J = 0.6, 2.4 Hz), 10.10 (1H, d, J = 0.6 Hz).

Bis(6-chloro-3-pyridylmethyl)amine (6). Colorless crystals; mp 71—72 °C; IR (KBr) 1455, 1095, 811 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.73 (1H, br), 3.81 (2H, s), 7.30 (2H, d, J = 8.1 Hz), 7.68 (2H, dd, J = 2.4, 8.1 Hz), 8.33 (2H, d, J = 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ = 49.8, 124.2, 134.3, 138.8, 149.4, 150.4. HRMS. Found: *m/z* 268.0407. Calcd for $C_{12}H_{11}Cl_2N_3$: M, 268.0407.

Isolation of *N*-(6-Chloro-3-pyridylmethylene)-(6-chloro-3-pyridyl)methylamine (9). A mixture of the Raney nickel catalyst (Nikko Rica R-100, 2.0 g), 6-chloro-3-pyridinecarbonitrile (**5**) (2.0 g, 14.4 mmol), EtOH (24 mL), and 28% aqueous NH_3 (4.0 mL, 57.6 mmol) was stirred at 25 °C and atmospheric hydrogen pressure for 2—3 h and pale yellow solid was precipitated. The reaction mixture was filtered and the remaining pale yellow solid was dissolved with MeOH. MeOH was removed under reduced pressure and the residual solid was recrystallized from EtOH to give **9** (575 mg, 2.16 mmol). Colorless crystals; mp 99—101 °C; IR (KBr) 1585, 1454, 1105 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 4.84 (2H, s), 7.36 (1H, d, J = 8.1 Hz), 7.43 (1H, d, J = 8.1 Hz), 7.69 (1H, dd, J = 2.4, 8.1 Hz), 8.17 (1H, dd, J = 2.4, 8.1 Hz), 8.40 (1H, d, J = 2.4 Hz), 8.47 (1H, s), 8.68 (1H, d, J = 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ = 61.6, 69.3, 123.9, 124.2, 124.7, 130.3, 133.2, 137.1, 138.4, 149.0, 150.3, 158.6. HRMS. Found: *m/z* 266.0256. Calcd for $C_{12}H_9Cl_2N_3$: M, 266.0251.

Preparation of the Improved Raney Nickel Catalyst: Typical Procedure (R-38). To 25% aqueous NaOH (662 g, 4.14 mol) was added a 100 mesh sieved alloy powder (100 g, Ni 38%, Al 62%) at 80—90 °C and stirred well at 105 °C for 1 h. The upper layer was decanted with care not to let the catalyst flow away. The catalyst was washed with water and heated in water (800 g) at 98 °C for 2 h to give the improved Raney nickel catalyst, R-38.

Hydrogenation of 6-Chloro-3-pyridinecarbonitrile (4): Typical Procedure. A mixture of the Raney nickel catalyst (R-38, 4.5 g), 6-chloro-3-pyridinecarbonitrile (**4**) (30.0 g, 0.217 mmol), EtOH (257 mL), and 28% aqueous NH_3 (51.0 g, 0.839 mol) was stirred at 50 °C and 1.2—1.4 $kg\,cm^{-2}$ hydrogen pressure for 9 h. The mixture was filtered and washed with EtOH. The filtrate was analyzed by HPLC. The filtrate was concentrated under reduced pressure and the residual oil was subjected to kugelrohr distillation to give **1** boiling at 70—110 °C/1.0 mmHg (1 mmHg = 133.22 Pa) (22.6 g, 0.158 mmol, purity 96.0% by HPLC, 73% yield).

Analytically pure samples of **1** and **5** were obtained by fractional distillation of the crude reaction mixture through Vigreux distilling column.

3-Pyridylmethylamine (5).[16] Colorless liquid; bp 73—74 °C/1.0 mmHg; IR (neat) 3260, 1589, 1426 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.56 (br, 2H), 3.88 (2H, s), 7.23—7.27 (1H, m), 7.64—7.68 (1H, m), 8.47—8.50 (1H, m), 8.55 (1H, m).

6-Chloro-3-pyridylmethylamine (1). Colorless liquid; bp 105—107 °C/1.0 mmHg; IR (neat) 3350, 3330, 2970, 2950, 1570, 1560, 1445, 1100, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.40 (br, 2H), 3.67 (2H, s), 7.06 (1H, d, J = 8.1 Hz), 7.46 (1H, dd, J = 1.8, 8.1 Hz), 8.09 (1H, d, J = 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ = 42.9, 123.9, 137.3, 137.9, 148.5, 149.5. Found: C, 50.51; H, 4.90; N, 19.73%. Calcd for $C_6H_7ClN_2$: C, 50.54; H, 4.95; N, 19.65%.

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