

## Highly Selective Hydrogenation of 2-Chloro-5-cyanopyridine with an Improved Sponge Nickel Catalyst

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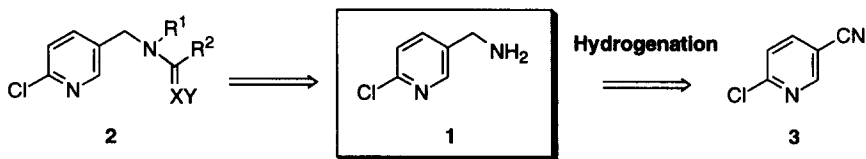
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**Abstract:** A practical synthesis of (6-chloropyridin-3-yl)methylamine (**1**), a key intermediate of neo-nicotinoide insecticides **2**, was achieved by highly selective hydrogenation of 2-chloro-5-cyanopyridine (**3**). The hydrogenation of **3** with an improved Sponge nickel catalyst, prepared from an alloy of low nickel content (Ni 38%, Al 62%) and subjected to heat treatment in water, was carried out at 50 °C and 1.2–1.4 kg/cm<sup>2</sup> hydrogen pressure to give **1** in 86% yield and (pyridin-3-yl)methylamine (**4**), a dechlorinated by-product, in only 2% yield. © 1999 Elsevier Science Ltd. All rights reserved.

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(6-Chloropyridin-3-yl)methylamine (**1**) is a key intermediate for the preparation of several neo-nicotinoide insecticides **2** that show strong insecticidal activities.<sup>1</sup> The development of a practical hydrogenation of 2-chloro-5-cyanopyridine (**3**), which is easily prepared by microbial hydroxylation of 3-cyanopyridine<sup>2</sup> followed by chlorination,<sup>3</sup> is highly attractive because of its commercial importance (Scheme 1).



Scheme 1

The hydrogenation of **3** with the ordinary Sponge nickel catalyst gave the desired amine **1** along with the generation of a large amount of dechlorinated primary amine **4**.<sup>4</sup> To decrease the generation of **4**, previously reported methods have employed high hydrogen pressure (100 kg/cm<sup>2</sup>), strictly anhydrous condition, and / or excess additives (NH<sub>4</sub>Cl), which are not favorable for large-scale preparation of **1** due to their complicated operation, strict safety controls, and high cost.<sup>5,6</sup> Therefore, we have attempted to develop a method which allows high yield and selectivity in aqueous condition without the use of additives, except NH<sub>3</sub>, at low hydrogen pressure.

The hydrogenation of **3** with commercially available Sponge nickel catalysts obtained from Nikko Rica

Corporation was investigated in EtOH and aqueous NH<sub>3</sub> at rt and atmospheric hydrogen pressure (Table 1, entries 1-4). The reduction proceeds stepwise through an aldimine and this is hydrolyzed under an acidic (pH 4.5) HPLC analysis condition and is detected as aldehyde **6**.<sup>7</sup> Among the commercially available catalysts examined, the use of R-205 prepared from an alloy of high nickel content (Ni 50%) by leaching at high temperature (105 °C, 1 h) showed the lowest dechlorination activity, but the dechlorinated amine **4** was generated in 10% yield (Table 1, entry 2).<sup>9</sup> Improved catalysts were prepared by heating in water (98 °C, 2 h) after leaching of aluminum to decrease the activity of the catalysts.<sup>10</sup> The use of R-41A prepared from an alloy of low nickel content (Ni 41%) showed lower dechlorination activity than the use of R-50 prepared from an alloy of high nickel content (Ni 50%), but the reaction rate at rt was very low and **4** was still generated in 5% yield (Table 1, entries 5 and 6).

**Table 1.** Hydrogenation of **3** with Various Sponge Nickel Catalysts<sup>a</sup>

Entry	Sponge Ni Cat.	Alloy		Leaching Condition <sup>c</sup>	Heat in Water	Yield (%)			
		Ni Cont. (%)	Particle Size (Mesh Pass)			1 <sup>d</sup>	4 <sup>d</sup>	5 <sup>d</sup>	6 <sup>d</sup>
1	R-200 <sup>b</sup>	50	150	90 °C, 1 h	-	68	15	5	<1
2	R-205 <sup>b</sup>	50	150	105 °C, 1 h	-	73	10	6	<1
3	R-100 <sup>b</sup>	41	100	90 °C, 1 h	-	65	20	5	<1
4	R-101 <sup>b</sup>	41	100	105 °C, 1 h	-	73	14	3	<1
5	R-50	50	200	105 °C, 1 h	98 °C, 2 h	77	7	4	<1
6	R-41A	41	200	105 °C, 1 h	98 °C, 2 h	75	5	3	8

<sup>a</sup> All reactions were performed using Sponge Ni (2.0 g), **3** (2.0 g), and EtOH (24 mL). <sup>b</sup> Commercially available from Nikko Rica Corporation. <sup>c</sup> 25% aq NaOH was used. <sup>d</sup> Characterization data are shown in ref. 8.

The improved catalysts were prepared from alloys of even lower nickel content (Ni < 40%) or by heating in water at even higher temperature (155 °C, 2 h) to further decrease the activity of the catalysts (Table 2). As it was

**Table 2.** Preparation of Various Improved Sponge Nickel Catalysts

Sponge Ni cat.	Alloy		Leaching Condition <sup>a</sup>	Heat in water
	Ni cont. (%)	Particle size (Mesh pass)		
R-41B	41	200	105 °C, 1 h	155 °C, 2 h
R-38A	38	200	105 °C, 1 h	98 °C, 2 h
R-38B	38	100	105 °C, 1 h	98 °C, 2 h
R-37A	37	200	105 °C, 1 h	98 °C, 2 h
R-37B	37	100	105 °C, 1 h	98 °C, 2 h

<sup>a</sup> 25% aqueous NaOH was used.

difficult to get fine particles of the alloy of low nickel content ( $\text{Ni} < 40\%$ ), 100 mesh sieved alloy powder was also used.<sup>11</sup> As the hydrogenation of **3** with R-41B and R-37A could not be completed at rt, these were carried out at 50 °C (Table 3, entries 1-4). Though R-41B showed the lowest dechlorination activity, the yield of **5** was increased (Table 3, entry 3). The use of R-37A gave **1** in high yield (81%) and showed low dechlorination activity without increase of the yield of **5** (Table 3, entry 4).

Optimization of the hydrogenation conditions (the amount of catalyst, temperature, and hydrogen pressure) using the improved catalysts prepared from the alloys of low nickel content ( $\text{Ni} < 40\%$ ) in a preparative scale was investigated to minimize the generation of **4** (Table 3, entries 5-8). In this optimization study, the amount of the catalyst was reduced to cut down the catalyst cost, and less than 2.0 kg/cm<sup>2</sup> hydrogen pressure was employed to carry out the hydrogenation without the use of an autoclave. When the hydrogenation of **3** (30 g) with R-38B (4.5 g) was carried out at 50 °C and 1.2-1.4 kg/cm<sup>2</sup> hydrogen pressure, the best result was obtained to give **1** in 86% yield and the yield of **4** was decreased to 2% (Table 3, entry 8). This reaction mixture was filtered, concentrated, and purified by kugelrohr distillation to give **1** in 73% isolated yield with 96.0% purity (Table 3, entry 8).<sup>12</sup>

**Table 3.** Hydrogenation of **3** with Various Improved Sponge Nickel Catalysts<sup>a</sup>

Entry	Sponge Ni cat.	Cat. (g) / <b>3</b> (g)	Hydrogen pressure (kg/cm <sup>2</sup> )	Time (h)	Yield (%)			
					<b>1</b>	<b>4</b>	<b>5</b>	<b>6</b>
1 <sup>b</sup>	R-50	1.0	a. p. <sup>d</sup>	1.5	62	17	3	1
2 <sup>b</sup>	R-41A	1.0	a. p. <sup>d</sup>	2.0	71	15	2	1
3 <sup>b</sup>	R-41B	1.0	a. p. <sup>d</sup>	5.0	75	3	8	5
4 <sup>b</sup>	R-37A	1.0	a. p. <sup>d</sup>	1.5	81	8	2	2
5 <sup>c</sup>	R-37A	0.15	1.2-1.4	7.0	81	2	1	1
6 <sup>c</sup>	R-37B	0.15	1.2-1.4	11.0	77	2	3	3
7 <sup>c</sup>	R-38A	0.15	1.2-1.4	9.0	81	2	1	2
8 <sup>c</sup>	R-38B	0.15	1.2-1.4	9.0	86 (73 <sup>e</sup> )	2	2	<1

<sup>a</sup> All reactions were performed in the presence of 28% aq NH<sub>3</sub> (4 equiv) at 50 °C. <sup>b</sup> Sponge Ni (4.0 g), **3** (4.0 g), and EtOH (48 mL) were used. <sup>c</sup> Sponge Ni (4.5 g), **3** (30 g), and EtOH (204 g) were used. <sup>d</sup> a. p. = atmospheric pressure. <sup>e</sup> Isolated Yield.

The characterizations of the various improved Sponge nickel catalysts are summarized in Table 4. The catalysts prepared from the alloys of low nickel content and fine particles showed low aluminum content. In the catalyst of low aluminum content, the crystallization of the nickel crystallite easily proceeded by heat treatment in water to enlarge its size. The enlargement of the crystallite size decreases the BET (Brunauer-Emmett-Teller) surface area<sup>13</sup> of the catalyst, which results in decrease of the dechlorination activity. The dechlorination activity decreased in the following order R-50 > R-41A > R-37A, R-37B, R-38A, R-38B > R-41B which show an approximately linear correlation with the BET surface area.

In conclusion, a practical synthesis of (6-chloropyridin-3-yl)methylamine (**1**) was achieved by highly selective hydrogenation of 2-chloro-5-cyanopyridine (**3**) with an improved Sponge nickel catalyst, prepared from an alloy of low nickel content ( $\text{Ni} 38\%$ ) and subjected to heat treatment in water (98°C, 2 h), at 50 °C and 1.2-1.4kg/cm<sup>2</sup> hydrogen pressure. This method has a number of practical advantages: 1. no need of an expensive high-pressure autoclave, additives except NH<sub>3</sub>, and strict safety controls; 2. the employment of low

**Table 4.** Characterization of Various Improved Sponge Nickel Catalysts

Sponge Ni cat.	Al cont. (%)	Crystallite dimension (Å)	BET area (m <sup>2</sup> /g-Ni)
R-50	6.3	69	63
R-41A	4.6	88	55
R-41B	3.7	125	28
R-38A	3.2	110	39
R-38B	3.3	102	46
R-37A	3.5	104	44
R-37B	3.3	111	40

temperature, low hydrogen pressure, and aqueous conditions, and was successfully applied to a multi-hundred kilogram scale synthesis of **1**.

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- (8) **1**: bp 101-102 °C/1.0 mmHg; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.50 (br, 2H), 3.90 (2H, s), 7.30 (1H, d, *J* = 8.1 Hz), 7.67 (1H, dd, *J* = 2.4, 8.1 Hz), 8.34 (1H, d, *J* = 2.4 Hz). **4**: bp 73-74 °C/1.0 mmHg; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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, s). **5**: mp 72 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.73 (1H, br), 3.81 (4H, 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). **6**: mp 70-71 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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, 0.6, 2.4 Hz), 10.10 (1H, d, 0.6 Hz).
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- (12) Hydrogenation of **3** with R-38B: A mixture of R-38B (4.5 g), 2-chloro-5-cyanopyridine (**3**) (30.0 g, 0.217 mol), EtOH (204 g), and 28% aqueous NH<sub>3</sub> (52.5 g, 0.868 mol) was stirred at 50 °C and 1.2-1.4 kg/cm<sup>2</sup> hydrogen pressure for 9 h. The mixture was filtered and washed with EtOH. The filtrate was concentrated under reduced pressure and the residual oil was subjected to kugelrohr distillation (up to 110 °C/1.0 mmHg) to give **1** (22.6 g, 0.158 mol, purity 96.0% by HPLC, 73% yield).
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