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# An Improved Process for Industrial Production of Isosorbide-5-mononitrate: Recycling of Wastes

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# An Improved Process for Industrial Production of Isosorbide-5-mononitrate: Recycling of Wastes

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Waste reduction, ~90%, area, 100 kg-scale



# ABSTRACT

Different recovery schemes were studied for the wastes generated during the industrial production of isosorbide-5-mononitrate (IS-5-MN). For the wastewater, the disposal was achieved by hydrolysis of isosorbide-2-mononitrate (IS-2-MN) to the starting material isosorbide (IS) utilizing its alkaline environment, where NaOAc was also recovered in form of trihydrate effectively. For the solid waste, two different schemes including direct crystallization and catalytic hydrogenation had been investigated. The former one afforded useful isosorbide dinitrate (ISDN) efficiently, and the latter one provided an efficient and scalable route to synthesize IS-5-MN from ISDN. The combinations of unit operations were evaluated on 100-kg scale, and had been proved feasible and robust. The waste recycling strategy provided an eco-friendly and recyclable complement for the industrial-scale preparation of IS-5-MN, which minimized the waste emission during the process.

Keywords: Isosorbide-5-mononitrate, waste recycling, catalytic hydrogenation, scalable

# **1. INTRODUCTION**

Isosorbide-5-mononitrate (IS-5-MN) is an organic nitrate drug for the cardiovascular disease treatment, and has been widely used across the world due to its prominent pharmacokinetic properties.<sup>1-2</sup> Over the past few decades, plenty of methods have been explored to synthesize IS-5-MN, which could be summarized into 3 strategies (**Scheme** 1): **a**. Direct nitration of isosorbide (IS) with concentrated nitric acid or acetyl nitrate.<sup>3-5</sup> **b**. Selective reduction of isosorbide dinitrate (ISDN), which was obtained by the complete nitration of IS.<sup>2, 6-10</sup> **c**. Nitration at C-5 of a C-2 protected IS, and the protecting group was eliminated subsequently to obtain IS-5-MN.<sup>11-13</sup>

Scheme 1. General synthetic strategies employed to study IS-5-MN



Unfortunately, none of the methods above was efficient enough to the industrial-level production owing to disadvantages including low selectivity, low yield or expense.<sup>14</sup> Considering the cost and the operability, the direct nitration method has been adopted to produce IS-5-MN in our company during the past twenty years. However, the inevitable side products including nitrated impurities (~40%) and a small amount of acetylated impurities (total, ~3%, see Supporting Information for details) were generated during the direct nitration process. Hence, additional purification steps were required. The current work-up was designed according to the different solubility of the compounds (**Figure** 1, black solid line): after neutralizing the reaction mixture, the water insoluble component ISDN was removed by filtration. Then, an aqueous solution of sodium hydroxide was added into the filtrate to form sodium IS-5-MN hydrate<sup>5</sup>, which was salted out with a high purity. Subsequently, target compound could be obtained by an acidification process.

Although the route had provided considerable profit, the large quantity of wastes (solid waste & wastewater) had caused significant environmental pressure, especially the production capacity of IS-5-MN was increased to100 tons/year. In order to reduce the waste emission, a better way for waste disposal should be examined for greener and sustainable development. Herein, we would like to provide our recent waste-treatment investigation of the IS-5-MN procedure.



Figure 1. Process flow chart of IS-5-MN and waste recycling

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<sup>2.</sup> RESULTS AND DISCUSSION

The investigation was commenced with the analysis result of the wastes, which was listed in **Table** 1. For each 100 kg of product, about 1730 kg of wastewater and 38 kg of solid waste were generated. IS-2-MN and unreacted IS comprised the main organic part of the wastewater, and the remaining part were inorganic compounds including NaOAc and NaOH. Meanwhile, the main component of the solid waste was ISDN.

Waste type	Total quantity/kg	Main component	Quantity/kg
		IS-2-MN	32
Wastewater	1730	IS	12
		NaOAc	406
		NaOH	63
Solid waste	38	ISDN	35

Table 1. Quantity of waste generated per 100 kg of IS-5-MN

#### 2.1. Treatment of the wastewater

As shown in the **Table** 1, the complex composition of the wastewater included the organic derivatives of IS and inorganic salts, which made the direct recovery of compounds difficult. Fortunately, IS-2-MN could be hydrolyzed to IS in alkaline conditions. Thus, the wastewater's high pH environment was exactly suitable for the hydrolysis of IS-2-MN to afford the starting material IS (**Figure** 1, green solid line). According to the results (**Table** 2, see Supporting Information for details), the hydrolysis rate was dependent on the reaction temperature. The reaction rate was too slow at low temperature (0 °C and 20 °C), where the transformation could hardly be achieved (entries 1-2, **Table** 2). Although higher temperatures could promote the process (entries 4-5, **Table** 2), a series of impurities would generate. Therefore, a milder temperature of 50 °C was employed for the hydrolysis of IS-2-MN.

Purity<sup>b</sup>/% Entry<sup>a</sup> Temperature/°C Time IS-2-MN IS total impurities 10 d 33.6 65.8 0.6 5 d 22.1 71.5 6.4 8.0 h 1.9 90.8 7.3 4.5 h 80.3 19.7 1.6 h \_ 73.5 26.5

 Table 2. Effect of temperature on the hydrolysis of IS-2-MN

<sup>a</sup>Conditions: each 500 mL wastewater;

<sup>b</sup>Detected by GC (based on area normalization).

Subsequently, the hydrolysis solution was neutralized with acetic acid so that NaOAc and IS were the main component. After the concentration of the solution, crystallization for NaOAc was examined according to their different solubility in the 95% EtOH. It was found that industrial-grade NaOAc $\cdot$ 3H<sub>2</sub>O could be recovered leaving the highly soluble IS in the filtrate. A simple optimization was conducted for the optimal crystallization condition (**Table** 3). The results showed that the recovery rate was higher at lower crystallization temperature, but room temperature (25 °C) was a preferred choice considering the energy consumption. Increasing the solvent usage would result in a decline in the recovery rate. Therefore, the condition listed in entry1, **Table** 3 was considered as the optimal choice. Finally, the high purity IS was recovered by vacuum distillation (140-160 °C, 10-18 mmHg) affording a recovery rate of 55%, which could be used directly as the starting material.

Table 3. Conditions for the recovery of NaOAc

Entry <sup>a</sup>	Solvent/mL	Temperature/°C	Yield/%	Content <sup>b</sup> /%
1	50	25	86	58.6
2	50	15	87	58.3
3	50	5	91	58.0
4	75	25	81	58.8
5	100	25	68	59.1
6	100	15	72	59.0
7	100	5	79	58.9

<sup>a</sup>Conditions: each 120 g wastewater was concentrated to give a paste-like mixture, solvent (95% EtOH);

<sup>b</sup>Detected by potentiometric titration, theoretical content: 60.3%.

#### 2.2. Treatment of the solid waste

#### 2.2.1. Recovery of ISDN from the solid waste

Considering the major solid waste component ISDN was also an organic nitrate drug, attempts were paid to recover it as active pharmaceutical ingredient (API) by direct crystallization (**Figure** 1, blue solid line). A panel of solvents were screened and the results were listed in **Table** 4. It was found that water could give an excellent yield, but the purity could hardly reach our requirement (entry 1, **Table** 4). Acetone and EtOH gave considerable purity during the test, however, their poor yield made methanol as the optimal solvent due to its high yield and purity.

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<b>Table</b> 4. Conditions for the crystallization of ISDN from the solid waste
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Entry <sup>a</sup>	Solvent	Amount /mL	Temperature/°C	Yield/%	Purity <sup>b</sup> /%
1	H <sub>2</sub> O	4000 <sup>c</sup>	20-30	93.4	91.5
2	MeOH	200	0-5	85.9	99.0
3	EtOH	250	0-5	78.5	97.3
4	95% EtOH	300	0-5	82.4	96.2
5	Acetone	150	0-5	58.6	98.4

<sup>a</sup>Conditions: each 100 g solid waste;

<sup>b</sup>Detected by HPLC, chromatograms could be found in Supporting Information; <sup>c</sup>Trituration.

# 2.2.2. Recovery of IS-5-MN from the solid wastes

Despite the excellent recovery rate of ISDN from the solid waste, it should be noted that the clinical demand of ISDN was shriveled during the years, which may be due to its side-effect. As estimated, the ISDN recovered from the solid waste would reach 28 tons/year, which could exceed the market demand easily. Previously, selective transformation from ISDN to IS-5-MN had been reported (**Scheme** 1, strategy **b**).<sup>4-10</sup> Therefore, it was highly attractive to obtain IS-5-MN from the solid waste. After literature survey, catalytic hydrogenation was chosen as our strategy considering industrialization and environmental pressure.

Previous study had shown the 5-endo group of ISDN was more crowded than the 2-exo group, where the reduction at the latter position was dominant.<sup>14</sup> However, considerable quantity of IS-2-MN and IS were generated during our initial attempts using Pd/C as catalyst<sup>15</sup> (entry 1, **Table** 5). The ratio of IS-5-MN/IS-2-MN was merely 2.5:1, and the yield of IS-5-MN was less than 40%. Fortunately, although IS was still found, significant increase of the ratio and the yield of IS-5-MN were observed when passivated catalyst was used (entry 2, **Table** 5). The positive results indicated the lower activity of the catalyst reduced 2-exo nitro group selectively rather than the stereo-hindered 5-endo one. Subsequent screening showed the Lindlar catalyst such as Pd/BaSO<sub>4</sub> and Pd/CaCO<sub>3</sub> gave considerable selectivity, where IS-5-MN could be obtained in an acceptable yield (~60%). Considering the cost and the efficiency, Pd/CaCO<sub>3</sub> was used as the optimal choice. After hydrogenation, the side products IS-2-MN and IS were merged into the wastewater and recovered according to the method described in section 2.1 (**Figure** 1, blue dotted line).

 Table 5. Conditions for the catalytic hydrogenation of the solid waste

Entry <sup>a</sup>	Catalyst	Time/h	Content <sup>b</sup> /%	5-MN/2-MN	Yield <sup>c</sup> /%
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			ISDN	IS-5-MN	IS-2-MN	IS		
1	Pd/C	3.0	0.5	50.4	20.2	27.7	2.5:1	38.2
2	$Pd/C^d$	3.6	0.8	62.5	6.8	25.2	9.2:1	49.9
3	Lindlar <sup>e</sup>	2.0	0.4	71.6	5.0	20.7	14.3:1	58.3
4	Pd/BaSO <sub>4</sub>	4.0	0.8	62.6	5.6	25.4	11.2:1	50.6
5	Pd/CaCO <sub>3</sub>	1.5	1.0	70.1	4.9	22.9	14.3:1	58.2

<sup>*a*</sup>Reaction conditions: solid waste (10.0 g), solvent (95% EtOH, 200 mL), temperature (25 °C), catalyst (0.6 g), pressure (8 atm):

<sup>b</sup>Detected by GC, corresponding chromatograms could be found in Supporting Information;

<sup>c</sup>Isolated yield of IS-5-MN;

<sup>d</sup>Passivated Pd/C<sup>16</sup>;

<sup>e</sup>Lindlar catalyst: 5% Pd/CaCO<sub>3</sub>/PbO (dry), 0.2g.

Subsequently, the recyclability of this catalytic system was examined. Unfortunately, it was found that the reaction time was prolonged dramatically, where the Pd leaking was significant (nearly 15%) comparing with the moderate rate of 2% in the blank control (entries 1-3, **Table** 6). Further investigation of this hydrogenation process showed that the solution was acidic (pH=5-6) and NO<sub>2</sub><sup>-</sup> (detected by anion chromatography) was accumulated during the hydrogenation. It was deduced that the nitrous acid, reductive intermediate state of nitrate ester, was not converted to nitrogen immediately. Thus, the weak acidic environment corroded calcium carbonate leading to the Pd leaking. To suppress the Pd leaking, four common-used bases were tested to neutralize the acid generated during the transformation, and considerable improvements were observed (entries 4-7, **Table** 6). However, strong base (e.g., NaOH) would mediate the hydrolysis of IS-5-MN affording a lower yield (entry 6, **Table** 6). Therefore, the weak base NaHCO<sub>3</sub> was used as the optimal choice. Further examination of the recyclability indicated Pd/CaCO<sub>3</sub> could be used at least 5 times without significant losing of activity (entry cycle, **Table** 6).

Table 6. The Pd leaking rate and the screening of bases to suppress the leaking

Entra	Catalyst	Paco <sup>b</sup> Pu	Dung	Runs Time/h _	Loss rate of I	Viold <sup>d</sup> /0/	
Enuy		Dase	Kulls		Experiment	Blank	
1			$1^{st}$	1.5	14.5	1.2	58.2
2	Pd/CaCO <sub>3</sub>		$2^{nd}$	4.5	13.8	1.4	60.4
3			3 <sup>rd</sup>	8.0	11.2	2.3	58.1
4	Pd/CaCO <sub>3</sub>	Et <sub>3</sub> N	$1^{st}$	1.0	4.2	1.5	58.6
5		Na <sub>2</sub> CO <sub>3</sub> <sup>e</sup>	$1^{st}$	1.0	2.8	1.6	55.4

	6		NaOH	$1^{st}$	0.8	3.1	2.2	49.5
	7		NaHCO <sub>3</sub>	$1^{st}$	1.2	2.0	1.3	60.6
-				$1^{st}$	2.0	2.2		62.6
				$2^{nd}$	2.2	2.8		63.4
	Cycle <sup>f</sup>	Pd/CaCO <sub>3</sub>	NaHCO <sub>3</sub>	3 <sup>rd</sup>	2.6	2.5		61.5
				4 <sup>th</sup>	3.0	2.7		60.8
				5 <sup>th</sup>	3.5	3.1		59.7

<sup>*a*</sup>Reaction conditions: solid waste (10.0 g), solvent (95% EtOH, 200 mL), catalyst (0.6 g), temperature (25 °C), pressure (8 atm);

<sup>b</sup>Base (40 mmol);

<sup>c</sup>Detected by Inductively Coupled Plasma Mass Spectrometry (ICP-MS);

<sup>d</sup>Isolated yield of IS-5-MN;

<sup>e</sup>Base (20 mmol);

<sup>f</sup>100 g-scale, the filtered catalyst was reused in the next batch without additional purification.

# 2.3. Evaluation of combination of different treatment of wastes

After the investigation of the separate treatment of the wastes, the unit operations were combined to propose two waste recycling strategies: (A) section 2.1 & section 2.2.1: treatments were independent, where ISDN was recovered from the solid waste and the wastewater was treated as mentioned above. (B) section 2.1 & section 2.2.2: IS-5-MN was recovered from the solid waste via catalytic hydrogenation, while the side products (IS-2-MN and IS) were combined together with the wastewater for further treatment. To prove the assumptions, two combinations were verified both on 100-kg scale. It was found that these proposed combinations were feasible and robust. The results listed in the **Table** 7 showed that valuable products were recovered effectively and waste emissions were reduced to a minimum level.

Route <sup>a</sup>		Pr	oduct/kg	Waste emission/kg		
Route	IS-5-MN	IS	ISDN	NaOAc·3H <sub>2</sub> O	Solid waste	Wasterwater
А	-	18.7	28.6	695.5	6.5	56.7
В	15.4	25.1	-	680.0	3.8	106.0

Table 7. Quantity of recovered products and waste emissions after recycling

<sup>a</sup>Conditions: wastes generated per 100 kg of IS-5-MN production.

In addition, the overall consideration about the process employed for industrial usage was evaluated. The first combination was simpler and practical than the second one. However, the recovered ISDN would face the problem of oversupply. While for the second process, the overall consumption of reagents and energy was higher than the first one. Considering the market demand, the optimal process maybe incorporate both routes, where some solid waste was treated to provide marketing required amount of ISDN, and the rest part was treated by the second process, which will maximize the economical result.

#### **3. CONCLUSION**

In summary, the wastes generated during the direct nitration route of IS-5-MN production was investigated. Different methods were designed to recover or convert organic wastes to useful substance. The treatment of the solid waste could provide either ISDN by crystallization or IS-5-MN by catalytic hydrogenation, the latter also provided a practical and scalable protocol for synthesis of IS-5-MN according to strategy **b**. The wastewater was heated for hydrolysis of undesired IS-2-MN to recover the IS. Meanwhile, inorganic salt was effectively recovered from the wastewater. The combination of these unit operation provided potential schemes for comprehensive treatment of wastes and was tested on pilot scale. Although both schemes provide considerable reduction in wastes, the flexible adjustment of combination of both schemes should be the optimal choice, which depended on the market demands of ISDN. Despite the highly selective nitration of IS will be the ultimate solution for the IS-5-MN preparation, the work provided an efficient and practical procedure for the waste treatment at current stage.

### **4. EXPERIMENTAL SECTION**

General information. The wastes were collected from Shandong New Time Pharmaceutical Co., Ltd., Linyi, China. All the catalysts (palladium content, 5%; water content, 65.1-67.7%) were purchased from Kaili catalyst & materials Co., Ltd., Xi'an, China. Other materials, solvents, and reagents were purchased from commercial sources and were used without further purification. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded using a Bruker 600 MHz spectrometer. Chemical shifts ( $\delta$ ) are expressed in ppm downfield from the internal standard TMS. Mass spectra was recorded on an Agilent 1290/6540B UHPLC-QTOF/MS. GC was performed on GC-2014C equipped with DB-1 column (30 m × 0.25 mm × 1.00 µm). GC parameters: initial temperature 160 °C, hold time 10 min, ramp 50 °C/min, final temperature 220 °C, hold time 8 min. Palladium content was detected by Thermo Scientific<sup>TM</sup> iCAP Q ICP-MS. Analytical HPLC (Dionex UItiMate 3000 HPLC) analysis was carried out using a C18 reversed-phase (RP) column (150 mm × 4.6 mm, 5 µm) and detected at 210 nm, eluting with 25:75 MeOH/H<sub>2</sub>O at 1.0 mL/min. Anion chromatography analysis was carried out using a Dionex Ion<sup>TM</sup> AS11 column (4 × 250 mm) and detected at 210 nm, eluting with 4.5 mmol/L Na<sub>2</sub>CO<sub>3</sub>-0.8 mmol/L NaHCO<sub>3</sub> at 1.0 mL/min. Content of the NaOAc

was detected by Professional Titrando Potentiometric Titrator (Metrohm 888).

Attention: the solid waste (specific ingredient, ISDN) is an **explosive** compound, avoiding vigorous agitation and high temperature (>170 °C, lit.<sup>17</sup>).

# Isosorbide dinitrate (ISDN)<sup>18</sup>

Solid waste (1.50 kg) was added to MeOH (3.0 L), heated at reflux and stirred (200 rpm) for 30 min, and then the mixture was cooled to 5 °C, the product which precipitated was filtered of, dried to give a white solid (1.28 kg, 85.3%), with a purity of 99.04%. Mp: 69.8-70.8 °C; LCMS (ESI): Calcd for [M+HCOO]<sup>-</sup>: 281.03; Found: 281.02; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  5.42-5.36 (m, 2H), 5.01 (t, *J* = 5.4 Hz, 1H), 4.59 (d, *J* = 5.2 Hz, 1H), 4.18-4.10 (m, 2H), 4.08 (dd, *J* = 11.4, 2.6 Hz, 1H), 3.94 (dd, *J* = 11.4, 5.5 Hz, 1H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$  85.4, 85.0, 81.7, 80.9, 71.8, 69.6.

# Isosorbide-5-mononitrate (IS-5-MN)<sup>19</sup>

Solid waste (540.0 g), 95% EtOH (10 L), NaHCO<sub>3</sub> (176.0 g) and Pd/CaCO<sub>3</sub> (31.0 g) were added to a 30L autoclave (equipped with rupture disc, 12 atm). After three vacuum/N<sub>2</sub> cycles to remove air, the stirred mixture was hydrogenated at 25 °C, 8 atm, 250 rpm. After the reaction completed (ISDN<1.0%), the catalyst was filtered off. The solvent was evaporated to give a residue, which was dissolved in ethyl acetate (2 L) and H<sub>2</sub>O (500 mL), the organic phase was separated and the aqueous layer was extracted with ethyl acetate (2 × 2 L), the combined organic phase was dried over sodium sulfate and filtrated, the filtrate was concentrated to give crude product, a white needle-shaped solid (241.0 g, 59.9%, dried under reduced pressure at 60 °C for 8 h) was obtained by crystallization (CHCl<sub>3</sub>), with a purity of 98.85% (CHCl<sub>3</sub> residue, about 20 ppm. Pd residue <10 ppm). Mp: 90.6-91.0 °C; LCMS (ESI): Calcd for [M+HCOO]<sup>-</sup>: 236.04; Found: 236.04; Calcd for [M-H]<sup>-</sup>: 190.03; Found: 190.03; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  5.35 (td, *J* = 5.5, 2.7 Hz, 1H), 5.00 (t, *J* = 5.2 Hz, 1H), 4.41 (d, *J* = 4.8 Hz, 1H), 4.36 (dd, *J* = 5.2, 2.7 Hz, 1H), 4.00 (dd, *J* = 11.3, 2.6 Hz, 1H), 3.97-3.90 (m, 2H), 3.88 (dd, *J* = 11.3, 5.5 Hz, 1H), 2.04 (d, *J* = 5.4 Hz, 1H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$  88.8, 81.4, 81.2, 75.8, 75.6, 69.2.

# Sodium acetate trihydrate and Isosorbide (IS)

Wastewater (1200 g) was heated and hydrolyzed at 50 °C (monitored by GC, IS-2-MN<1.0%), the reaction solution was neutralized with acetic acid and was concentrated<sup>20</sup> to give a past-like residue (492

g), the residue was added in 95% EtOH (500 mL), heated under slight reflux to dissolve, after cooling to 25 °C, the product which precipitated was filtered of, dried to give a pale white solid (419 g), with a content of 59.44% (calculated as NaOAc). Mp: 58.5-60.5 °C. A light yellow oil (13.4 g, solidified rapidly at room temperature), with a purity of 98.01%, was recovered from the filtrate by vacuum distillation (140-160 °C, 10-18 mmHg). Mp: 61.2-62.8 °C; Mass found: Calcd for  $[M+Na]^+$ : 169.05; Found: 169.05; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  4.66 (t, *J* = 4.9 Hz, 1H), 4.43-4.35 (m, 2H), 4.34-4.27 (m, 1H), 3.98 (d, *J* = 10.0 Hz, 1H), 3.91 (dd, *J* = 10.0, 3.3 Hz, 1H), 3.86 (dd, *J* = 9.5, 6.0 Hz, 1H), 3.56 (dd, *J* = 9.5, 5.8 Hz, 1H), 2.83 (d, *J* = 7.0 Hz, 1H), 2.56 (d, *J* = 4.6 Hz, 1H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$  88.1, 81.6, 76.6, 75.7, 73.5, 72.2.

#### **5. GENERAL METHOD**

The solvent (95% EtOH and MeOH) used in the waste treatment was recycled by simple distillation. In addition, the distillation residue and new wastes generated during the waste recycling process were disposed of in our company's sewage treatment station.

#### 6. ASSOCIATED CONTENT

Supporting Information available: The corresponding description of the acetylated side products. The relevant GC chromatograms in **Table** 2, **Table** 5 and HPLC chromatograms in **Table** 4. <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, MS spectrum for compounds IS-5-MN, ISDN, IS.

#### 7. AUTHOR INFORMATION

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Note: The authors declare no competing financial interest.

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(19). For 100-kg scale, the operation was carried out in a stainless steel hydrogenation kettle (2 m<sup>3</sup>) equipped with alarm device for temperature/pressure and automatic interlock protection device. The stirring speed was 200 rpm. Precision filtration with titanium rod (0.45  $\mu$ m tandem 0.22  $\mu$ m) was used in the catalyst hydrogenation route.

(20). For 100-kg scale (wastewater,  $\sim 2 \text{ m}^3$ ), falling film evaporator was used in the concentration process.