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Hydrogenation of 5-Alkylidene-2,4-Thiazolidiones on Pd/C Catalysts Under Mild Conditions: An Alternative Synthesis Route to Pioglitazone

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Abstract The hydrogenation of 5-alkylidene-2,4-thiazolidiones was studied using Pd/C to establish an alternative process for pioglitazone synthesis. The reportedly sluggish reactivity was due to the high reaction temperature in formic acid. The conditions were improved to 1 atm at 296 K, which results in a quantitative product with a smaller amount of the catalyst.

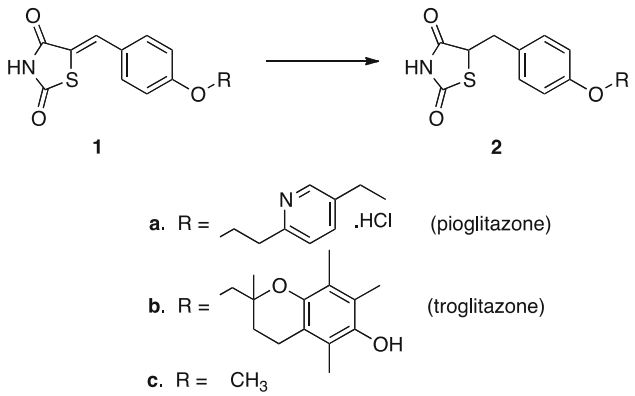
Keywords Pioglitazone · Hydrogenation · Catalyst deactivation · Formic acid · Palladium catalyst

1 Introduction

Tiazolidine analogues include effective drugs for noninsulin-dependent diabetes mellitus. Among the numerous analogues studied as medicines, currently pioglitazone (**2a**) [1] is commercially available, and troglitazone (**2b**) [2] was available until 10 years ago. These analogues may be obtained by the condensation of 2,4-thiazolidinedione and the corresponding 4-alchoxybenzaldehyde followed by the selective saturation at 5-exo-olefin (**1** to **2** in the scheme); however, this simple process has not been adopted for the practical production of **2a** [3]. The major drawback appears to be the saturation process. In the literature, the hydrogenation conditions for **1a** are typically 50 kg cm^{-2} at 323 K in DMF, which give only 65 % yield of **2a** [4]. The catalyst employed therein was a large amount of Pd black in a substrate/Pd with a molar ratio of 2.8 (mol/mol) [4]. A quantitative reaction was only reported with a specially prepared polymer-incarcerated Pd at room temperature, although the substrate/Pd molar ratio of 3 was still low [5]. Similar results have been reported in patents [6–10],

Where the reactions were performed under pressured hydrogen (5–10 kg cm^{-2}) at 323–353 K with palladium supported on activated carbon (Pd/C) or Pd black under low substrate/Pd molar ratios of 5–16, which resulted in 60–85 % yields. Homogeneous hydrogenations with an Rh complex and $NaBH_4$ reductions have also been reported [11].

In this report, we address the essential problem of this process and describe the development of a new hydrogenation procedure for this system using a commercial Pd catalyst supported on activated carbon.



Reduction of 5-alkylidene-2,4-thiazolidiones (1) to give 2

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2 Experimental

2.1 Materials

Substrate **1a** was obtained from Tokuyama Corp (mp = 443.9–444.6 K) and used for most runs. In some cases, **1a** was used after being recrystallized (mp = 445.8–446.1 K). Substrate **1c** was prepared from 2,4-thiazolidione and *p*-anisaldehyde and was recrystallized from a mixture of THF and toluene following the reported method [6]; **1c**: 92.7 % yield, pale-yellow solid, mp = 493.5–493.6 K. ^{1}H NMR data were identical to the reported values [12]. In this study, the 5 % Pd/C employed was 53 % wet STD-type (N.E. Chemcat, Japan) and was stored at 280 K until use. The activated carbon support had a BET surface area of 1,007 $m^2\ g^{-1}$, and the Pd surface area was 339 $m^2\ g^{-1}$. Palladium was distributed uniformly throughout the carbon particles (size = 23 μm) with 76 % dispersion. The other Pd/C catalysts were obtained from N.E. Chemcat (AER type, 1 % STD type, Pd/Al_2O_3, and ASCA) and from Kishida Chemicals, Japan (10 %). The ASCA type is known as a Pd–Pt (4.5 + 0.5 %) bimetallic catalyst.

2.2 Apparatus

Hydrogenation was performed under atmospheric pressure using a temperature-controlled water bath, an efficient magnetic stirrer (1,200 rpm), and a proper burette to measure the consumption of hydrogen gas. ^{1}H NMR data was recorded on a JEOL ECA-600 using $CDCl_3$ as a solvent and as an internal standard (δ 7.24). HPLC analysis was conducted with an ODS column (YMC-ODS-A, 4.6 mm i.d. × 150 mm), and 1.0 mL gradient elution was performed with CH_3CN/0.1 M NH_4OAc/AcOH = 100/100/4 to 120/80/3. Amounts of **1** and **2** were determined at 269 nm, and were calibrated. Other side products were estimated to have similar absorption coefficients to **2**, and were not calibrated. Conversion (%) was calculated as 100 × **2**/(**1** + **2** + others).

2.3 Hydrogenation

Wet 5 % Pd/C (46.4 mg, 22 mg of the actual amount, 1 mg as Pd) and solvent (4 mL) was placed in a flat bottom flask (50 mL). The solvent used was toluene, 1,4-dioxane, ethanol, or HCOOH. Hydrogen was charged, and the reaction mixture was then stirred for 15 min at 296 K. In some cases, the flask was heated at 353 K for 30 min and subsequently cooled to 296 K. A solution (6 mL) of the substrate (typically 1.0 mmol, 356 mg **1a**) was charged into the flask ($[subst]_{init}$ = 0.1 M), and the reaction course was monitored by HPLC, of which results were confirmed by ^{1}H NMR and hydrogen consumption measurements. The initial hydrogenation rate was determined around 15–25 % conversion. The hydrogenation of **1c** was performed in a manner similar to that of **1a**.

3 Results and Discussion

Pd/C is a widely applicable and popular catalyst for hydrogenation. Highly dispersed Pd metal particles on carbon supports with extremely high surface areas show prominent characteristics such as high activities, reproducible high turnover numbers, and mostly undetectable metal leaching into the product solution. In particular, Pd metal particles of STD-type Pd/C catalyst are highly dispersed, with a mean diameter of 1.4 nm.

Because **1a** is poorly soluble in many solvents, except in hot and highly polar solvents, systematic studies on the effects of solvent and temperature for the hydrogenation of **1a** are rare. Thus, we first studied a simpler and highly soluble analogue **1c** that is essentially identical to **1a** at the hydrogenation site. With the model substrate **1c**, the effect of the hydrogenation conditions could be investigated without the solubility problem inherent to **1a**. The hydrogenation of **1c** was performed in various solvents starting at room temperature. First, the reaction was performed with **1c**/(Pd/C)/solvent = 235 mg (1.0 mmol)/43 mg Pd/C (Pd: 10 μmol)/10 mL; the results are shown in Fig. 1. The reactions, except for those performed in ethanol, were slow but proceeded smoothly at 296 K. This result is somewhat surprising because all the reported hydrogenations of **1a** used elevated temperature of 323–353 K [6–10]. However, the hydrogenation in ethanol was an exception, which was rapid in the initial stage, although the conversion of **1c** could not exceed 10 % accompanying with the characteristic smell of hydrogen sulfide. These preliminary experiments suggest that hydrogenation potentially proceeds at room temperature irrespective of the solvent polarities; however, as observed in the case of ethanol, suppression of the catalyst deactivation during the reaction is a key factor for achieving a good yield from the overall reaction. Considering poor dissolving ability of toluene, 1,4-dioxanes showing the moderate dissolving power and acceptable reactivity was selected for the following reactions.

The temperature dependence of the hydrogenation of **1c** was studied in 1,4-dioxane, and the results obtained at 296–353 K are shown in Fig. 2. At the highest temperature of 353 K, the initial rate was the fastest; however, the hydrogenation quickly became sluggish and was almost interrupted after 25 h, with a conversion less than 25 %. The interruption was less pronounced at 333 K; however, the rapid reaction did not continue after the conversion reached 20 %, and the total conversion after 48 h was less than that achieved at 313 K, which reached 40 %. The

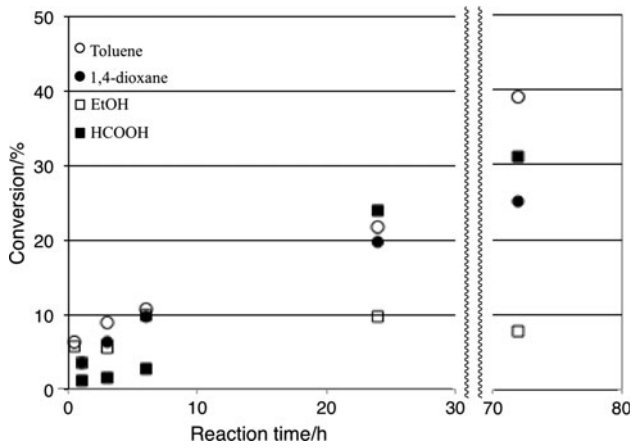

Fig. 1 Conversion/% of the hydrogenation of **1c** under the standard conditions (**1c**/Pd/solvent = 1.0 mmol/10 μmol/10 mL at 296 K) in different solvents

catalyst during the hydrogenation should be poisoned by a compound generated from the reactant. The poisonous compound must be some sulfur compound, but MS analysis as well al ^{1}H NMR analysis of the reaction mixture did not suggest any structural information during and after the hydrogenation in ethanol and in dioxane at elevated temperature. Overall, the decomposition problem became apparent even at 333 K, and a reaction temperature of 313 K resulted in the fastest kinetics for the reaction of **1c**, even though the initial rate ($r = 0.6$ mmol h^{-1} g^{-1}) was slower than that at 333 K ($r = 1.5$ mmol h^{-1} g^{-1}).

A high concentration of the substrate, which indicates the use of a smaller amount of solvent, may also be desirable in industrial applications. We studied the concentration effects with **1c** in dioxane in two ways: the solvent ratio was varied while the substrate/Pd molar ratio was maintained at 20, and the substrate ratio was varied while the catalyst and solvent amounts were fixed at 10 μmol/10 mL (both at 296 K). Figure 3 shows the initial rate and conversion after 24 h for the hydrogenation of **1c** with a constant substrate/Pd molar ratio. As long as the substrate/Pd molar ratio was kept constant, the initial rate was not significantly affected by the amount of the solvent. Figure 4 shows the initial rate and conversion after 72 h for the reaction with varied amounts of **1c**. The initial reaction rate of 5 mmol g^{-1} h^{-1} at a substrate/Pd molar ratio of 10 greatly decreased as the amount of the substrate was increased, and the rate calculated as a function of the amount of catalyst appeared to become constant at a low substrate/Pd molar ratio of 100 (0.1 M). The conversion was also drastically affected, and 100 % conversion of **1c** was attained at a low substrate concentration (<0.02 M), as shown in Fig. 4. We concluded that a full conversion was not achievable even after 72 h, when the substrate/Pd molar ratio was greater than 40.

A comparison of the results in Figs. 3 and 4 reveals that the substrate/Pd molar ratio is a critical factor for the hydrogenation of **1c**. This result is not attributable simply to reaction kinetics, such as the Langmuir–Hinshelwood mechanism, that assumes the strong adsorption of **1c** onto a Pd metal surface, as expected from the results in Fig. 4 (a negative reaction order with **1c**), because the reaction rate is relatively high and almost constant with a constant concentration of **1c** in the same concentration range (0th order with **1c**, Fig. 3). As previously suggested, sulfur poisoning of the Pd metal surface due to the partial decomposition of **1c** might cause the deactivation of the catalyst even at 296 K and become critical at a substrate/

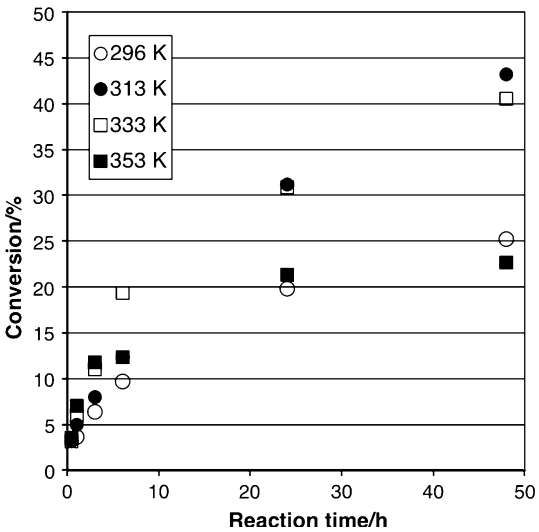

Fig. 2 Temperature dependence of the hydrogenation of **1c** in dioxane (**1c**/Pd/dioxane = 1.0 mmol/10 μmol/10 mL)

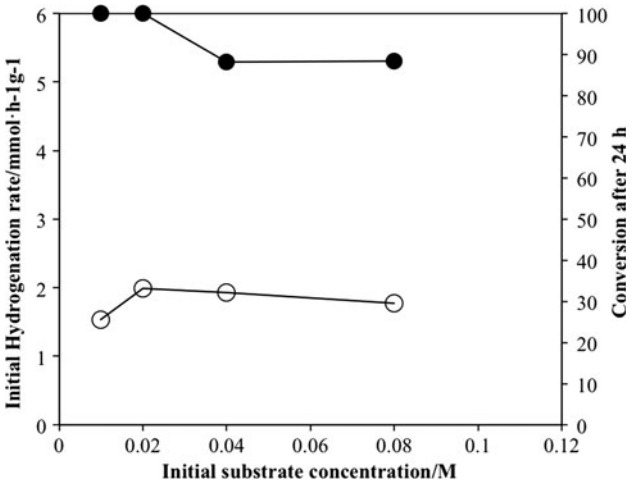

Fig. 3 Initial reaction rate (*open circle, left* axis) and conversion (*filled circle*, *right* axis, after 24 h) for varied amounts of the solvent 1,4-dioxane, which ranged from 2.5 to 20 mL, under fixed amounts of **1c** (0.2 mmol) and the catalyst (Pd: 10 μmol) at 296 K

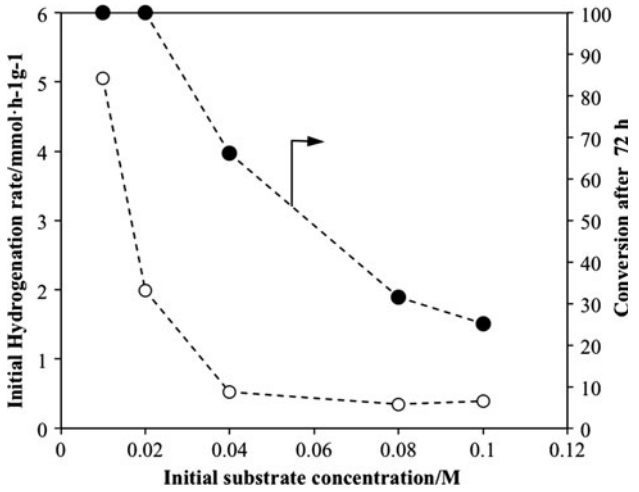

Fig. 4 Initial reaction rate (*open circle*, *left* axis) and conversion (*filled circle*, *right* axis, after 72 h) for varied amounts of **1c**, which ranged from 0.1 to 1 mmol, under fixed amounts of the catalyst (Pd: 10 μmol) and 1,4-dioxane (10 mL) at 296 K

catalyst molar ratio greater than 40. Another possibility is that this result was due to coking by the decomposition of **1c** during hydrogenation.

With the basic properties of **1c** in hand, the target molecule **1a** was studied next. To clarify the difference between **1a** and **1c** in the reactivity, the hydrogenations of **1a** and **1c** were compared under a high catalyst-ratio condition of substrate/Pd/HCOOH = 0.14 mmol/10 μmol/10 mL; the results are summarized in Table 1. Notably, **1a** and product **2a** were not fully soluble in formic acid, even under such low substrate-concentration conditions. Surprisingly, the reactivity of the hydrogenation of **1a** on Pd/C was high compared with that of **1c** (>100 times), even though the reaction sites were similar. Because the purity of the substrate can affect the initial reaction rates, the difference was confirmed with a 1:1 mixture (total 0.28 mmol, run 3) and a 2:1 mixture (total 0.42 mmol, run 5) of **1a** and **1c**. The reaction of **1a** was still rapid; however, the reaction of **1c** was suppressed to one-tenth or one-fourth the rate of **1a**, which indicated that **1a** and/or product **2a** adsorbed onto the catalyst more strongly than **1c**. More precisely, the suppression of the hydrogenation of **1c** was greater with **2a** (1/30–1/80) than with **1a**. We concluded that the existence of the 2,5-disubstituted pyridinium unit increased the adsorption strength and interrupted the hydrogenation of the 5-alkylidene of the 2,4-thiazolidinedione of **1c** and that the degree of this disruption was much stronger with **2a** than with **1a**; i.e. the adsorption strength decreases in the order **2a** > **1a** > **1c**, and thus the hydrogenation of **1a** proceeds by overcoming the interruption by **2a**.

Figure 5 shows the result of the hydrogenation of **1a** as a function of the initial substrate concentration. At a low concentration of 0.014 M, the hydrogenation of **1a** was 100

Table 1 Initial hydrogenation rate and reaction conversion for the reaction of **1a**, **1c**, and their mixture

Run	**1a** (mmol)	**1c** (mmol)	r_0 (**1a**)[a]	Conv. (**1a**) (%)	r_0 (**1c**)[a]	Conv. (**1c**) (%)
1	–	0.14	–	–	1.6	>99[b]
2	0.14		>184	99[b]	–	–
3	0.14	0.14	73	90[c]	0.14	30[c]
4	(0.14)[d]	0.14	–	–	0.02	49[c]
5	0.28	0.14	>184	84[c]	0.42	45[c]
6	(0.28)[d]	0.14	–	–	0.06	34[c]

Hydrogenation was performed at a substrate/Pd/HCOOH ratio of 0.14 mmol/25 μmol/10 mL at 296 K

[a] Initial hydrogenation rate (mmol g^{-1} h^{-1}) determined by ^{1}H NMR

[b] After 1 h

[c] After 6 h

[d] The product **2a** was added to the hydrogenation of **1c**

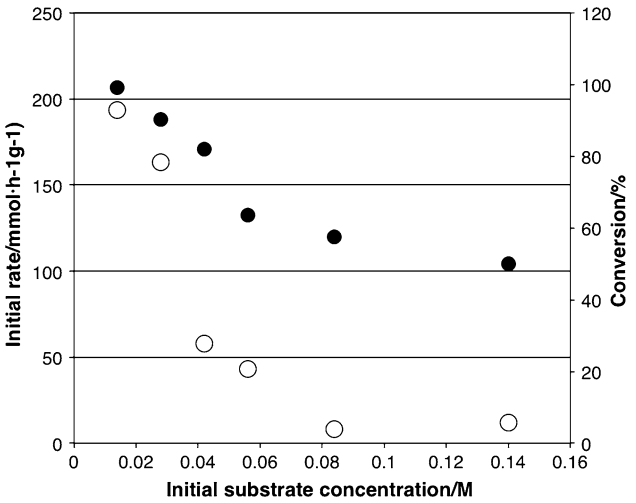

Fig. 5 Initial reaction rate (*open circle*, *left* axis) and conversion (*filled circle*, *right* axis, after 6 h) for the hydrogenation of **1a** at a **1a**/Pd/HCOOH ratio of 0.14–1.4 mmol/10 μmol/10 mL at 296 K

times faster than that of **1c** at the initial stage (Table 1). However, the decrease in the rate was dramatic, and the complete conversion of **1a** with a substrate/catalyst ratio greater than 50 was difficult to achieve. Apparently, the characteristics of the hydrogenation of **1a** include the rapid formation of **2a** and its rapid deactivation. Notably, the disubstituted pyridininium in **1a** was inert for the hydrogenation in all cases.

In addition to the 5 % STD-type Pd/C, several commercial Pd catalysts were examined for the hydrogenation of **1a**. As shown in Table 2, 5 % STD-type Pd/C exhibited a distinctly rapid initial hydrogenation rate and an optimal conversion after 6 h. However, at least under these conditions, a very rapid initial hydrogenation rate did not lead to a high conversion, which suggests that more active hydrogenation catalysts deactivate more rapidly. Overall,

Table 2 Hydrogenation of **1a** on Pd catalysts

Entry	Catalyst	r_0 (mmol g^{-1} h^{-1})	Conversion[a] (%)
1	5 % STD-type Pd/C (50 mg)	58	82
2	5 % AER-type Pd/C (50 mg)	10	75
3	Pd/Al_2O_3 (50 mg)	4.8	69
4	10 % Pd/C (25 mg)	7.0	57
5	1 % STD-type Pd/C (250 mg)	6.4	77
6	5 % ASCA-2-type Pd–Pt/C (50 mg)	7.5	61

Hydrogenation was performed at 296 K in formic acid on the substrate 1a/Pd (or Pd + Pt for ASCA-2)/solvent = 0.42 mmol/25 μmol/10 mL

[a] After 6 h

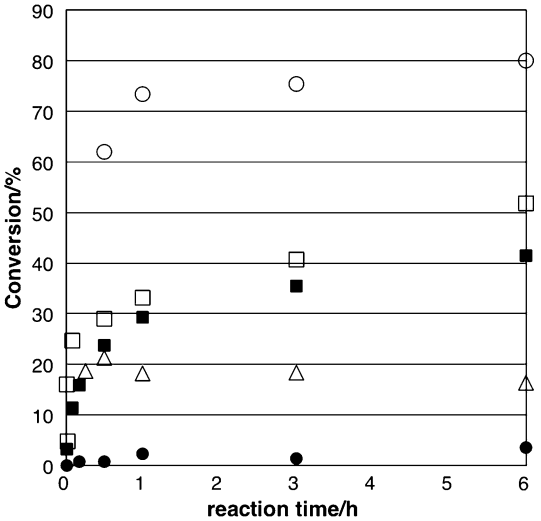

Fig. 6 Conversion of **1a** for hydrogenation under a **1a**/Pd/solvent ratio of 0.42 mmol/10 μmol/10 mL at 296 K (a) in HCOOH (10 mL) (*open circle*), (b) hydrogen pretreatment in HCOOH (10 mL) at 353 K (*filled circle*), (c) after a pretreatment in dioxane (2 mL) at 353 K and the subsequent HCOOH (8 mL) addition at 296 K (*open square*), (d) in dioxane (2 mL) without the pretreatment and then HCOOH (8 mL) (*filled square*) at 296 K, and in a mixture of dioxane (2 mL) and HCOOH (8 mL) (*open triangle*) at 296 K

the type of Pd catalyst does not significantly affect the reaction conversion.

The reaction conditions were further tuned in some extent. The reaction of **1a** at 5–10 MPa in an autoclave increased the hydrogenation rate, but the degree is within twofold. The recrystallization of **1a** may lead to a higher initial hydrogenation rate to some extent (30–60 %), but the improvement in the reaction rate did not last for a prolonged period, and the rates eventually became the same during the reaction.

Lastly, time profile of the hydrogenation of **1a** in formic acid at room temperature (296 K) was given in Fig. 6 (open circles). It is seen that the hydrogenation of **1a** is smooth under the optimized conditions. As suggested for the hydrogenation of **1c**, decomposition of **1a/2a** is a possible catalyst poisoning mechanism at elevated temperature. However, the contribution of the poisoning may not be dominant factor in the hydrogenation of **1a** in formic acid; i.e. when Pd/C in formic acid was warmed at 353 K under hydrogen for 30 min and then cooled and used for the hydrogenation of **1a** at 296 K, the catalytic activity decreased by less than 1/100 (closed circles). The catalyst heat treatment in dioxane did not deactivate the catalysis so much (open squares vs. closed squares). These findings clearly indicate that Pd/C is drastically deactivated by formic acid when heated at 353 K, and this decrease is probably a major reason for the slow hydrogenation of **1a** after the heat treatment in HCOOH at 353 K.

4 Conclusions

In the present study, the hydrogenation conditions of 5-alkylidene-2,4-thiazolidiones (**1a**) were established using Pd/C for an alternative process for pioglitazone (**2a**) synthesis. The optimized conditions (1 atm at 296 K) result in a quantitative product **2a** with a smaller amount of the catalyst than that reported until now. **1a** is poorly soluble in many solvents, and warm formic acid is the only applicable solvent if a biologically safe and properly volatile solvent is desired. The slow and sluggish kinetics of reported examples are mainly due to the deactivation of the Pd catalyst that results from the heating of Pd in formic acid. The formation of poisonous compounds by partial decomposition of the reactant and/or product may be responsible for the slow hydrogenation at high substrate/catalyst ratios. As a result, we established a synthesis process for **2a** in a quantitative yield via the hydrogenation of **1a**.

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