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Optimization and Scale-Up of a Novel Process for 2-Aminoindan Hydrochloride Production

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Abstract:

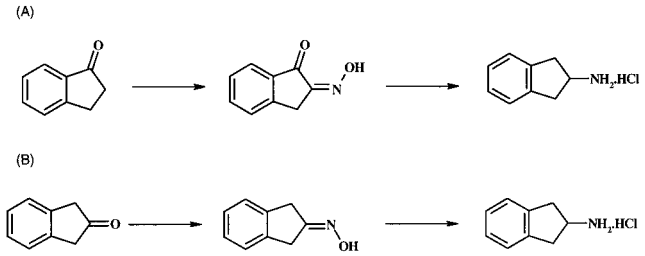
The need for an economical process for producing 2-aminoindan hydrochloride, a key starting material in manufacturing novel bioactive molecules, motivated development of a novel synthetic route using an inexpensive reactant, ninhydrin. The synthesis, involving oximation of ninhydrin followed by catalytic reduction of the resulting oxime intermediate to give 2-aminoindan, was demonstrated successfully, and a product purification scheme was developed to isolate 2-aminoindan as the hydrochloride salt form. Subsequent process development optimized the reduction step by identifying regimes of fast and slow reaction (corresponding to reduction of oxime and diketone functions, respectively), and tailoring reaction conditions to use mild conditions during the fast exothermic regime to ensure process safety followed by more severe conditions for the slower reaction. The process was successfully scaled up 100-fold in a pilot plant, with excellent yield and product quality agreement between laboratory and pilot plant.

Introduction

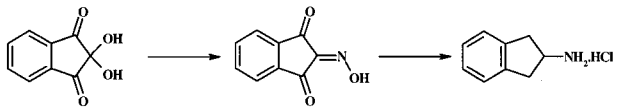
The difficulty in rapidly obtaining bulk amounts of 2-aminoindan hydrochloride, a key starting material in producing bioactive molecules, prompted an in-house evaluation and development of synthetic routes for its economical large-scale production. Literature preparations of the 2-aminoindan involve oximation of either 1-indanone[1] or 2-indanone,[2] followed by reduction of the oxime and ketone functions (Scheme 1). However, the relatively high costs of both 1-indanone and 2-indanone preclude their large-scale use as starting materials.

The structural similarity of ninhydrin to 1- or 2-indanone, its availability in bulk amounts (owing to its use as an analytical reagent for detecting primary amines[3]), and its low cost relative to that of 1-indanone and 2-indanone prompted evaluation of an analogous oximation/reduction sequence (Scheme 2) using ninhydrin. Preparation of the oxime by reaction of ninhydrin with hydroxylamine hydrochloride in ethanol has been reported previously.[4] The objectives of this work were thus to (a) demonstrate the synthetic feasibility of preparing 2-aminoindan hydrochloride from ninhydrin, (b) develop and optimize a process for scale-up in a pilot plant and commercial facility, and (c) demonstrate the process on a large scale and thus prove the synthetic utility of Scheme 2 for bulk-scale 2-aminoindan hydrochloride production.

Scheme 1. **Literature preparations of 2-aminoindan HCl salt using either 1- or 2-indanone**



Scheme 2. **Proposed 2-aminoindan hydrochloride preparation from ninhydrin**



Experimental Section

Apparatus and Materials. Process development experiments were performed using a Mettler-Toledo RC1 reaction calorimeter equipped with a 1-L jacketed glass vessel rated for 10-bar operation, a Hastelloy C pitched-blade agitator, a hydrogen gas reservoir, a pressure regulator for setting the reactor pressure, and valves for venting and purging (Figure 1). Calorimeter operating principles are discussed elsewhere.[5]

Sources and purities of materials used are given in Table 1. All materials were used as received. Although we used hydroxylamine in the salt form, the free base could undergo a runaway reaction leading to an explosion.[6] Two dry 10% Pd/C catalysts and two wet 10% Pd/C catalysts were investigated.

Reaction Monitoring and Product Analysis. For reaction monitoring, samples were analyzed by HPLC using a Hewlett-Packard Series 1000 HPLC equipped with a UV detector. Method details are given in Table 2.

In process development experiments, reaction calorimetry was also used to monitor reaction progress. During the

(1) Paul, H. *J. Prakt. Chem.* **1965**, *28*, 297; Nichols, D. E. *J. Med. Chem.* **1974**, *17*, 161−165; Cannon, J. G. *J. Med. Chem.* **1982**, *25*, 1442−1446; Johnson, M. P. *J. Med. Chem.* **1991**, *34*, 1662−1668.

(2) Levin, *J. Org. Chem.* **1944**, 380−386; Rosen, *J. Org. Chem.* **1963**, *28*, 2797−2801; Paleo, M. *Tetrahedron Lett.* **1994**, *11*, 3627−3638.

(3) *The Merck Index*, 12th ed.; Budavari, S., Ed.; Merck & Co.: Whitehouse Station, NJ, 1996; p. 1126.

(4) Paria, P. K., et al. *J. Indian Chem. Soc.* **1990**, *67*, 532.

(5) Girgis, M. J.; Kiss, K.; Ziltener, C. A.; Prashad, M.; Har, D.; Yoskowitz, R. S.; Basso, B.; Repic, O.; Blacklock, T. J.; Landau, R. N. *Org. Process Res. Dev.* **1997**, *1*, 339−349.

(6) Herman, S.; Zhenglong, X.; Sundareswaran, p. C.; Wang, Z. 218th ACS National Meeting, Book of Abstracts; American Chemical Society: Washington, DC, Aug. 22−26, 1999.

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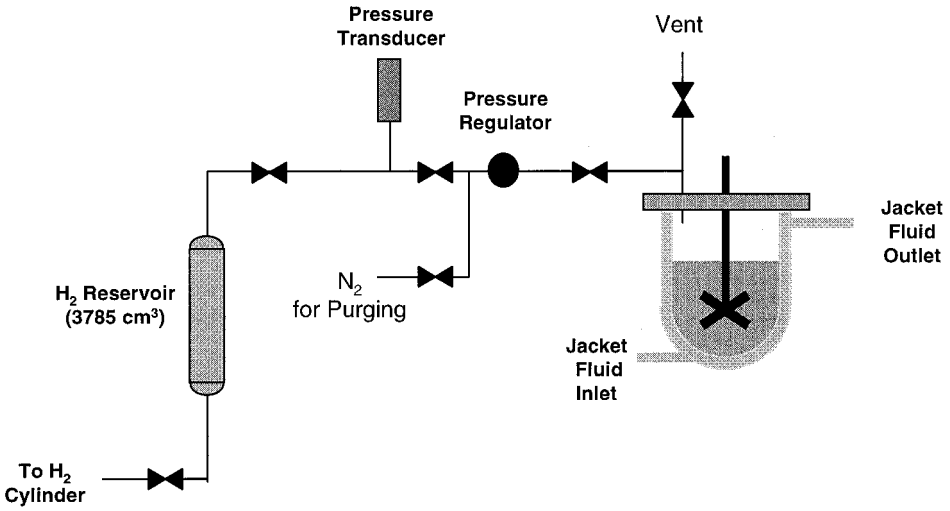


Figure 1. **Schematic diagram of RC1 calorimeter equipped for hydrogenation reactions.**

Table 1. **Sources and purities of materials**

material	molecular formula/CAS no.	source	purity %
ninhydrin	$C_9H_6O_4$, [485-47-2]	Aldrich	97
hydroxylamine hydrochloride	$H_2NOH{\cdot}HCl$, [5470-11-1]	Aldrich	99
hydroxylamine sulfate	$(H_2NOH)_2{\cdot}H_2SO_4$, [10039-54-0]	Aldrich	99
(A) dry 10% Pd/C	Pd [7440-05-3, 7440-06-4]	Aldrich	–
(B) dry 10% Pd/C	Pd [7440-05-3, 7440-06-4]	Aldrich	–
(C) 60% wet 10% Pd/C	Pd [7440-05-3, 7440-06-4]	Precious Metals Corp.	–
(D) 30% wet 10% Pd/C	Pd [7440-05-3, 7440-06-4]	Precious Metals Corp.	–
concentrated sulfuric acid	H_2SO_4 [7664-93-9]	Mallinckrodt	96.1
acetic acid glacial	CH_3CO_2H [64-19-7]	Mallinckrodt	99.7
hydrogen	H_2 [1333-74-0]	AGL	99.999

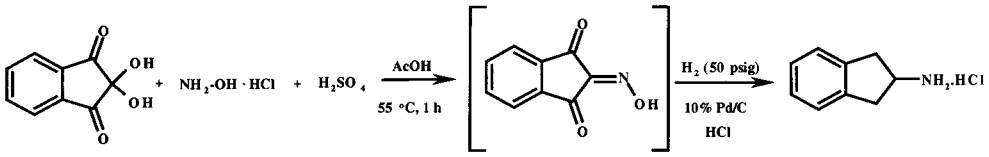
Table 2. **HPLC method for reaction monitoring**

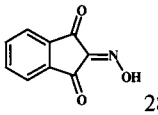
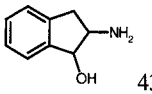
column	Waters Symmetry C-18, 15 cm, 4.6 μm particles
mobile phase	water (with 0.1% trifluoroacetic acid) and acetonitrile, with water/acetonitrile ratio initially 95:5 changing to 10:90 over 15 min
mobile phase flow rate, mL/min	1.5
wavelength used, nm	250
column temperature, °C	30

catalytic reduction, hydrogen consumption was determined by measuring the H_2 gas pressure inside the hydrogen reservoir, which had a known volume (3.785 cm^3) and was kept at room temperature (typically 25 °C).

Detailed Procedure. Charge the 1-L RC1 MP10 reactor with 33.00 g (0.185 mol) of ninhydrin and 554.70 g of glacial acetic acid. The reaction mixture is blue. Seal the reactor under an N_2 atmosphere. Add at 25 °C 54.42 g of sulfuric acid[1] with a dosing rate of 1 mL/min and 31.63 g of hydroxylamine sulfate. Keep the reactor under an N_2 atmosphere. Mix the reactor content using a stirring speed of 800 rpm. Heat the reaction mixture to 55 °C. Hold at 55 °C for 30 min. The process is endothermic. The reaction mixture turns from blue to yellow. The intermediate oxime precipitates. It is important not to overheat the reaction mixture because of a decomposition process starting at 84 °C. Cool to 25 °C and add a slurry of 2.64 g of dry 10% Pd on activated carbon premixed with 77.40 g of glacial acetic acid (*caution*: Dry Pd/C is flammable). Close the reactor and pressurize to 40 psig with N_2 and then depressurize. Repeat the cycle of 40 psig pressurization/depressurization with N_2 twice. Turn the stirrer off and then pressurize with hydrogen to 40 psig and depressurize. Repeat the cycle of 40 psig pressurization/depressurization with H_2 twice. Pressurize with hydrogen to 50 psig and test for leaks. If no leaks are found, depressurize to 20 psig. With the stirrer still off, open the hydrogen supply valve to the reactor. With the pressure on the reactor at 20 psig, turn the stirrer on (800 rpm). A maximum heat release rate of 35 W/kg is measured during the first 45 min. After 1 h at 25 °C and 20 psig, increase the pressure to 40 psig. Wait for 15 min and increase the batch temperature from 25 to 35 °C. HPLC analysis during the first 5 h reveals that the oxime intermediate is totally consumed after the first 3 h. The reaction is monitored by calorimetry and H_2 consumption. The heat flow attains a near-zero value, and H_2 consumption stops after about 8 h. After 10 h, close the hydrogen supply valve, stop agitation and vent to the atmosphere. Purge three times with nitrogen and open the reactor. Remove the slurry from the reactor. Charge the 9-cm Büchner filter with 20 g of Celite. Filter the reaction mixture. Wash the cake with 70 g of acetic acid (do not let the cake dry). Evaporate 550 mL of acetic acid

Table 3. **Reaction scheme and conditions used to demonstrate synthesis feasibility**



React.	$NH_2OH{\cdot}HC$ l mol/eq.	H_2SO_4 eq.	10% Dry Pd/C[a] w/w %	H_2 time h	2-aminoindan hydrochloride % yield	By-prod. % yield.
1	2	0	25	10	trace	n.d.
2	1	1.6	30	16	16	 28  43
3	1	3	40	6	52	 16
4	1	3	40	8	54	 7

under vacuum (20 mbar, 50−55 °C). Add 250 g of xylene and evaporate 300 mL of the xylene/acetic acid azeotropic mixture under vacuum (20 mbar, 50−55 °C). Add 170 g of xylene. Add at 25 °C under stirring 367 g of a 20% NaOH solution (exothermic, maintain the temperature below 55 °C). Measure the pH of the aqueous layer (pH paper). The pH must be above 11. If not, continue the basification with 20% NaOH until this pH value is reached. Separate the bottom aqueous layer for proper disposal. Filter the top organic layer. Add to the filtrate 51 g of a 4 N HCl solution in 1-pentanol (exothermic, maintain the temperature below 30 °C). Cool the resulting suspension to 0 °C and maintain this temperature for 1 h. Filter off the solids through a Büchner funnel equipped with a polypropylene pad and wash the cake once with 100 g of heptane. Dry the filter cake at 45−50 °C (100 ± 5 mbar) for 16 h to afford 19.14 g of 2-aminoindane hydrochloride (identical in all respects with the authentic sample) as a white solid, mp 241−242 °C (decomposition). Yield: 66%.

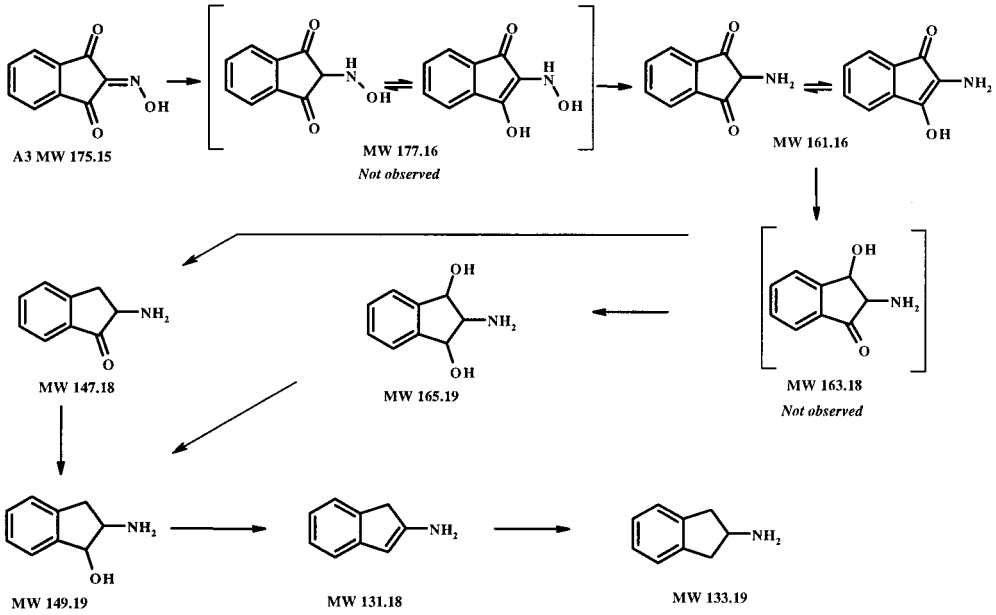
Results and Discussion

Process Development: Ninhydrin to 2-Aminoindan Hydrochloride. ***Demonstration of Synthetic Route.*** At the outset the aim was to produce 2-aminoindan hydrochloride via a one-pot synthesis, involving oximation of ninhydrin with hydroxylamine hydrochloride in glacial acetic solvent followed by reduction of the oxime and ketone functions. An initial attempt at conducting the reduction concurrently with the oximation by mixing ninhydrin and hydroxylamine hydrochloride in acetic acid, adding Pd/C catalyst and heating to 55 °C for 10 h under 50 psig of H_2 did not yield the desired product (Table 3, entry 1).

In subsequent experiments, the oximation was performed before the reduction step, with the oximation step carried out by heating ninhydrin and hydroxylamine hydrochloride at 55 °C in glacial acetic acid for 30 min, followed by cooling to room temperature. During this process the 2-oximino intermediate precipitated from the solution.

Using 1 equiv of hydroxylamine hydrochloride followed by reduction in the presence of 1.6 equiv of sulfuric acid as

Scheme 3. **Proposed reaction pathways for reduction of ninhydrin oxime to 2-aminoindan**



an additive (Table 3, entry 2) gave 2-aminoindan hydrochloride in 16% yield along with oxime diketone intermediate and 2-aminoindanol. A dramatic improvement was observed when 3 equiv of sulfuric acid were used (Table 3, entry 3), with the desired product formed in 52% yield after 6 h along with some 1-indanone byproduct. These conditions were found to be reproducible (Table 3, entry 4) and were used in subsequent process development.

The probable reduction reaction pathway (Scheme 3) was inferred on the basis of all intermediates identified by LC/MS in several experiments. Although intermediates in brackets were not detected, their presence is presumed, as they are necessary for understanding the formation of 2-aminoindan from ninhydrin oxime. The requirement for excess sulfuric acid is understandable if the two dehydration steps (MW 165.19 → 147.18 and 149.19 → 131.18), are assumed to be rate-determining. Hydrogenation without intermediate olefin formation may also occur from the intermediacy of aziridine (neighbouring group participation).

As basic nitrogen compounds can inhibit reactions occurring on metal catalysts by adsorbing strongly and blocking catalytic sites,[7] greater amounts of sulfuric acid equivalents could improve reaction performance by protonating the nitrogen compounds to decrease their extent of adsorption.

Product Isolation Optimization. As sulfuric acid is already present in the reaction mixture, the sulfuric acid salt of 2-aminoindan (Table 4, entry 1) was first isolated. Although isolation of the sulfuric acid salt gave good yield, it could not be used in the subsequent synthetic step. Attempts to isolate the free base led to degradations (Table 4, entry 2).

Subsequent product purification attempts focused on isolating the HCl salt. The main difficulty encountered was the formation of a strong emulsion upon basification with sodium hydroxide. To avoid this problem, acetic acid was first removed by azeotropic distillation with toluene (Table 4, entry 3). This approach was not so successful because azeotropic removal of acetic acid with toluene is not efficient (i.e., the toluene/acetic acid azeotrope contains 28% acetic acid), giving 2-aminoindan hydrochloride in only 44% yield. Using xylene instead of toluene gave a more favorable azeotrope (71% acetic acid), and thus more thorough removal of acetic acid, resulting in a clean separation between the aqueous and organic layers upon basification. After separation of the layers, 2-aminoindan hydrochloride was precipitated using a 4 N HCl in ethanol solution (Table 4, entry 4). This solution led to a layering and agglomeration of particles, rendering the filtration cumbersome. The use of HCl solution in 1-pentanol removed this problem (Table 4, entry 5). During the basification step, 20% NaOH appeared to be the optimum for saturating the aqueous layer. With these optimized conditions, 2-aminoindan hydrochloride was isolated in 66% yield (99% purity PAN, 96.69% ES).

Thus, a novel one-pot synthesis of 2-aminoindan hydrochloride from ninhydrin was demonstrated. This success motivated further process optimization with emphasis on investigating the impacts of H_2 pressure, temperature, amount of sulfuric acid, and Pd catalyst type during the reduction.

Process Optimization: Oxime Diketone Reduction. *Selection of Agitation Rate in Laboratory Experiments.* To obtain similar conversion rates between laboratory and pilot plant reactors, gas−liquid reactions must be performed in the same gas−liquid mass transport regime on both scales, especially if gas−liquid mass transfer limits the conversion rate. Gas−liquid mass transfer in the pilot plant vessel in which scale-up was planned was quantified by measurement of the volumetric mass transfer coefficient $k_L a$ at a typical agitation rate (150 rpm) as described elsewhere[8] and determined to be about 0.1 s^{-1}. The agitation rate in the RC1 vessel (800 rpm) was then selected to give a 0.1 s^{-1} $k_L a$ value. The same agitation rate was also employed for ninhydrin oximation, as it was sufficient to keep the precipitated oxime diketone intermediate suspended.

(7) Emmett, P. H. *Catalysis*; Reinhold Publishing Corporation: New York, 1954; Vol. I.

Table 4. **Product workup optimization**

react.	procedure[a]	comments	yield (%)	purity (%)
1	-azeotropic concentration (1-pentanol) until precipitation -filtration/drying	-sulfuric acid salt contaminated with inorganic salts.	67	99 (PAN)[b]
2	-poured into ice -basification (50% NaOH) -extraction (EtOAc)/concentration	-emulsion due to NaOAc -rapid degradation of 2-aminoindan as free base	n. d.	n. d.
3	-azeotropic concentration (toluene × 3) -dilution (H_2O)/ basification (50% NaOH) -extraction (toluene) -precip. (2.5 N HCl/EtOH) -filtration/drying	-emulsion due to NaOAc	44	95 (PAN)
4	-azeotropic concentration (xylene × 2) -dilution (H_2O)/ basification (NaOH 10%) -extraction (xylene) -precip. (4 N HCl/EtOH) -concentration/filtration/drying	-clear separation of aq./org. layers -large amount of NaOH required -layering and formation of agglomerates during concentration -darkening of material upon drying	70	87 (PAN)
5	-conc/azeotropic conc (xylene × 1) -basification (20% NaOH) -extraction (xylene) -precip. (4 N HCl/1-pentanol)/ cooling to 0 °C -filtration/drying	-clear separation of aq./org. layers -aq. saturated but homogeneous -clean precipitation of 2-aminoindan hydrochloride with homogeneous particle size (no layering)	66	99 (PAN) 95.7 (ES[c])

[a] Reaction mixture in all cases was first filtered over Celite. [b] PAN signifies "Peak Area Normalization." [c] ES signifies "External Standard."

Table 5. **Reaction conditions and product yield in initial process development experiments**

run	**oximation temperature** [°C]	**reduction temperature** [°C]	**reduction pressure** [psig]	**catalyst**[a] type w/w %	**composition** ninhydrin:hydroxylamine: H_2SO_4 [mol]	**loading** ninhydrin/solvent [g]	2-aminoindan hydrochloride % yield after workup
1	55	80	40	wet type C 100%	1:1 (NH_2OH·HCl):3	33/630	0
2	55	20	40	wet type D 40%	1:1 (NH_2OH·HCl):3	33/630	53
3	55	60	40	dry type B 8%	1:1.05 [$(NH_2OH)_2$·H_2SO_4]:3	33/630	n.d.
4	55	20	40	dry type B 8%	1:1.05 [$(NH_2OH)_2$·H_2SO_4]:3	33/630	70

[a] Catalyst designations are given in Table 1.

Concerns about the scale-up of hydrogenation of oxime diketone with at least some of the compound in the solid phase was of concern. This concern was resolved a posteriori by observing that the initial rate depended strongly on reaction conditions (e.g., temperature and pressure) and with the good agreement between laboratory and pilot plant results on scale-up, indicating that the solids dissolution rate was sufficiently large so as not to impact the overall conversion rate.

Impact of Catalyst Water Content and Reaction Temperature. Safety concerns about pilot plant use of dry Pd/C catalyst, which can ignite easily, prompted evaluation of wet Pd/C catalysts for the reduction. As a reaction time shorter than 8 h was also sought, higher reaction temperatures (vs room temperature) were also evaluated. Conditions for the initial process development experiments are shown in Table 5. Hydroxylamine hydrochloride was used in only the first two experiments, being replaced in later experiments with hydroxylamine sulfate because of corrosion concerns. In all cases, the mole ratio of ninhydrin:hydroxylamine salt was 1:1; thus, with the hydroxylamine sulfate, the number of hydroxylamine equivalents was doubled. In all cases, the oximation was performed by adding the hydroxylamine hydrochloride or hydrogen sulfate to a mixture of glacial acetic acid, ninhydrin, and sulfuric acid at 50 °C and maintaining at this temperature. Although the reaction is

(8) Delmling, A.; Karandikar, B. M.; Shah, Y. T.; Carr, N. L. *Chem. Eng. J.* **1982**, *29*, 127−140.

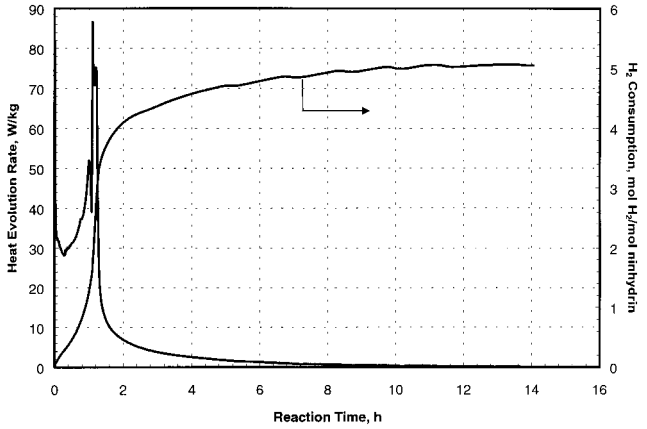


Figure 2. **Calorimetric and H_2 consumption profiles using wet Pd/C at 80 °C (run 1, Table 5).**

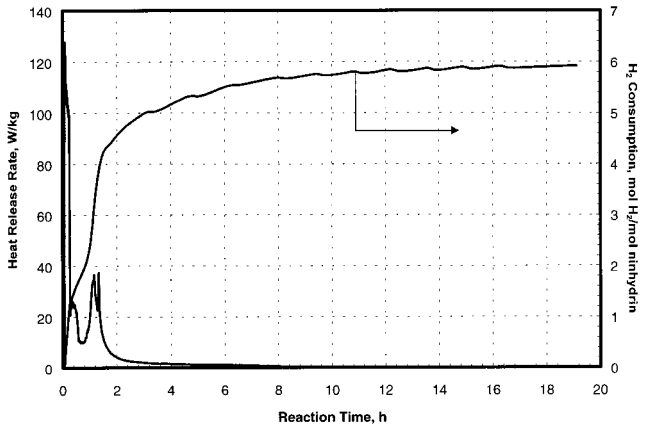


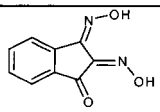
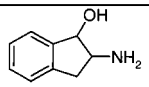
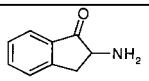
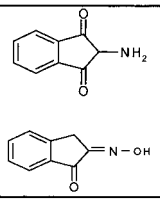
Figure 3. **Calorimetric and H_2 consumption profiles using wet Pd/C at 20 °C (run 2, Table 5).**

endothermic, causing a heat absorption of +120 kJ/kg, the short duration of the endothermic process (<1 min) did not cause temperature control problems upon scale-up.

A reduction temperature of 80 °C with a wet Pd/C catalyst gave a final hydrogen consumption of 5 mol H_2/mol ninhydrin (Figure 2). As complete reduction of the oxime diketone requires 6 mol H_2/mol ninhydrin (Scheme 2), incomplete reduction and formation of other products was inferred. HPLC analysis of the final reaction sample confirmed this inference, as it showed no formation of 2-aminoindan, with several other products being formed instead. The calorimetric profile shows a maximum at about 1.1 h, indicating an autocatalytic reaction.

Reduction at 20 °C using a wet Pd/C catalyst with a lower water content gave a final hydrogen consumption of about 6 mol H_2/mol ninhydrin (Figure 3). The 2-aminoindan hydrochloride yield after product isolation and purification, however, was only 53%. The low yield was consistent with detection of several byproducts in the final reaction mixture chromatogram. Examination of the proposed structures based on LC/MS of some of these (Table 6) indicates incomplete reduction, even though approximately 6 mol of hydrogen were consumed per mole of ninhydrin, and the reaction was stopped only after heat flow and hydrogen consumption both ceased (Figure 3). Evidently, unknown side reactions involving additional hydrogen consumption occurred. Unlike the

Table 6. **Presumed structures of some detected by-products**

Compound	Structure	Comments
2-3-dioxime 1-indanone		Non isolated intermediate
2-aminoindanol		By-product when using high temperature
2-aminoindanone		By-Product when using 0.54 eq of $(NH_2OH)_2 H_2SO_4$
$C_9H_7NO_2$		By-products in Run 2

previous experiment, which was performed at higher temperature and which gave essentially no aminoindan formation, the calorimetric profile in this case is characterized by a high initial heat release rate, followed by a region of lower heat release involving at least one autocatalytic reaction.

Since wet Pd/C catalysts of different water content used either near or above room temperature did not give the desired product in good yield, subsequent experiments focused on using dry Pd/C catalysts. Even with a dry Pd/C catalyst at 60 °C, a low yield of 2-aminoindan hydrogen sulfate was obtained, with 2-aminoindanol being the dominant product (Figure 4, Table 6). The incomplete reduction was consistent with a H_2 consumption below 6 mol H_2/mol ninhydrin. The calorimetric profile was also different than in the other runs.

Good (70%) 2-aminoindan yield was obtained by using dry Pd/C at 20 °C (run 4, Table 5, Figure 5). As the previous experiment which gave at least some 2-aminoindan formation (e.g., Figure 3) showed that a rapid and exothermic reaction occurred initially followed by a less exothermic reaction, run 4 was performed at a lower pressure (20 psig) initially with the pressure increased to 40 psig at 0.75 h, after the initial exothermic reaction ceased. The lower initial pressure slowed the initial rapid exothermic reaction to give a heat evolution rate of 35 W/kg, and thus within the estimated 60 W/kg heat removal rate of a commercial vessel;[9] the subsequent higher pressure gave a greater reaction rate during the slower part of the process. Subsequent HPLC and LC/MS analyses revealed that during the rapid initial reaction, most of the oxime was converted and that during the slow reaction regime (1−18 h), most of the ketone reduction occurred, with autocatalytic behavior occurring at about 5.2 h. At these conditions, good yields were obtained (70% isolated yield, >95% yield in the reaction mixture based on external standard) and with the expected H_2 consumption being slightly higher than the expected value of 6 (Figure 5).

The initial process development thus showed that using either wet or dry Pd/C catalyst, the reduction could not be

(9) Stoessel, F. *Course on Thermal Safety*; Summit, NJ, April 1998.

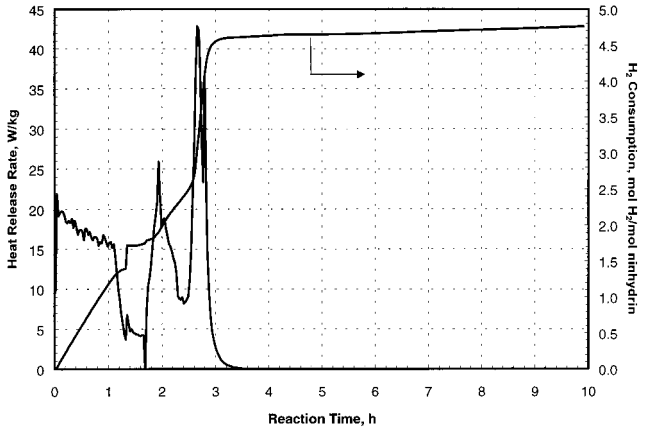


Figure 4. **Calorimetric and H_2 consumption profiles with dry Pd/C catalyst at 60 °C (run 3, Table 5).**

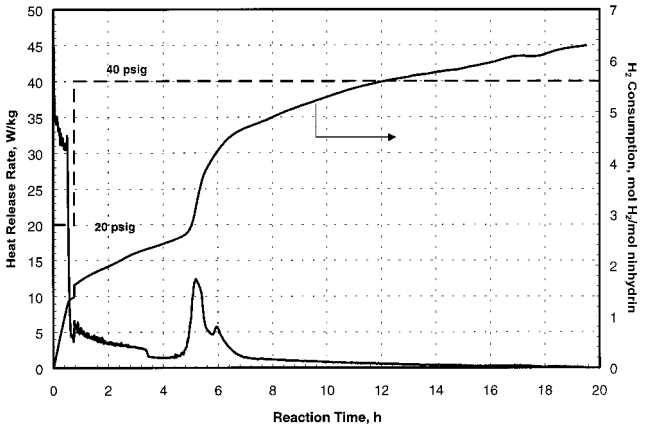


Figure 5. **Calorimetric and H_2 consumption profiles using dry Pd/C catalyst at 20 °C with 20−40 psig pressure ramp (run 4, Table 5).**

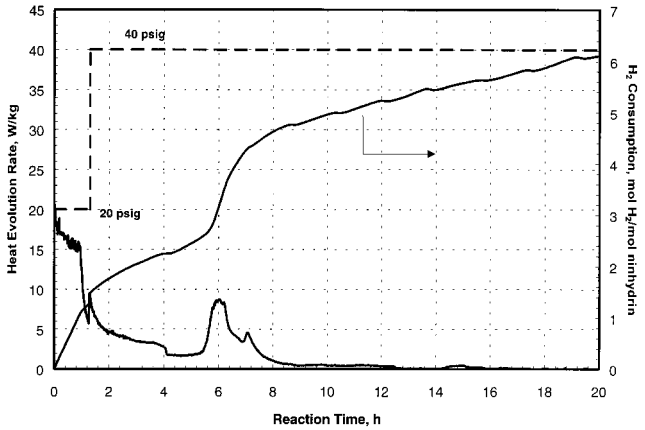


Figure 6. **Calorimetric and H_2 consumption profiles using dry Pd/C catalyst at 25 °C with a 20−40 psig pressure ramp (run 5, Table 7).**

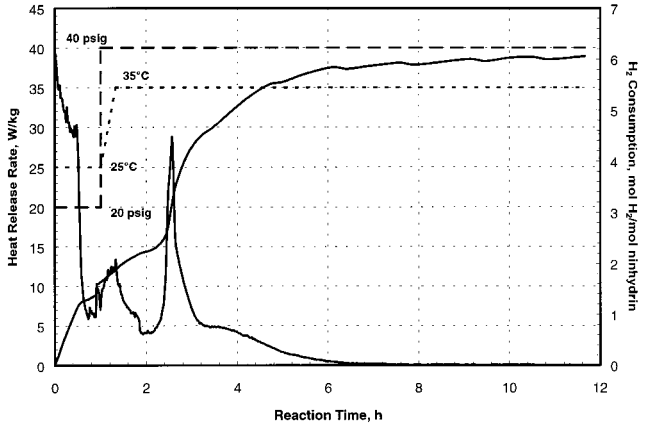


Figure 7. **Calorimetric and H_2 consumption profiles at optimized conditions. (run 6, Table 7).**

performed at higher temperatures (e.g., >60 °C). The best results were obtained using a dry Pd/C catalyst at 20 °C (i.e., near room temperature), although some desired product was also obtained using a wet Pd/C catalyst at 20 °C. In the two cases where 2-aminoindan was formed, similar calorimetric profiles were obtained, suggesting that the shape of calorimetric profile can give a rapid qualitative indication for at least some 2-aminoindan formation.

Reduction Optimization. Reaction optimization (Table 7) focused on shortening the reaction time by modifying the reaction pressure and temperature programs using the dry Pd/C catalyst available for scale-up in the pilot plant (Catalyst A, Table 1).

Run 5 (Figure 6) was designed to repeat the experimental conditions from run 4 (Figure 5), viz., using a 20 to 40 psig pressure increase after the initial exothermic reaction was completed, but at a slightly higher reaction temperature (25 vs 20 °C). The catalyst was evidently less active than that for run 4, as the rapid reaction terminated at 1.3 h (vs 0.75 before at a 5 °C lower temperature). Nevertheless, 2-aminoindan was produced in 91.3% yield based on external standard at a 20-h reaction time, with good 2-aminoindan hydrochloride yield (64%) obtained after workup (Table 8).

It was desirable to shorten the reaction time to under 16 h to allow performing the reduction in two pilot plant shifts. The ketone reduction (i.e., in the slow reaction regime) was thus performed at a higher temperature (35 °C) in the subsequent experiment (run 6, Table 7). Thus, a pressure increase from 20 psig to 40 psig was followed by a temperature increase over 20 min from 25 to 35 °C. With this modification, the reaction time was shortened to under 12 h (Figure 7).

Figure 7 shows that by performing the ketone reduction at 35 °C, the heat evolution rate arising from the autocatalytic reaction identified earlier increased significantly, with the maximum heat evolution rate at about 2.5 h being close to 30 kJ/kg. The autocatalytic process can also be detected by the inflection point (point of maximum slope) in the hydrogen consumption profile, which coincides with the heat evolution spike at ∼2.5 h. However, the small width of the profile due to the autocatalytic reaction results in an adiabatic temperature rise of 22 °C. This temperature rise does not pose a significant safety concern if loss of cooling occurred. A temperature rise due to the autocatalytic reaction would also not impact product quality significantly on the basis of process research experimental results, where temperature excursions as high as 40 °C occurred without significant product degradation. Final reaction conditions for the reduction were selected on the basis of run 6 (Figure 7), which gave an isolated 2-aminoindan hydrochloride yield of 66%.

Table 7. **Reaction conditions for reduction optimization**

run no.	oximation temperature [°C]	reduction temperature [°C]	reduction pressure [psig]	catalyst[a] type w/w %	composition ninhydrin: hydroxylamine sulfate: H_2SO_4 [mol]	loading ninhydrin/ solvent [g]	2-aminoindan hydrochloride % yield after workup
5	55	25	20−40	dry type A 8%	1/1.05/3	33/630	64%
6	55	25−35	20−40	dry type A 8%	1/1.05/3	33/630	66%
7	55	25−35	20−40	dry type A 8%	1/1.05/3	33/630	74%

[a] Catalyst designations are given in Table 1.

Table 8. **Results of final optimization runs**

run no.	reduction temperature [°C]	catalyst[a] w/w %	reaction time [h]	% yield of 2-aminoindan before work-up	% yield of 2-aminoindan·HCl after workup
5	25	dry type A 8%	20	91.3	64
6	25−35	dry type A 8%	12	93.7	66
7	25−35	dry type A 8%	8	94.1	74

[a] Catalyst designations are given in Table 1.

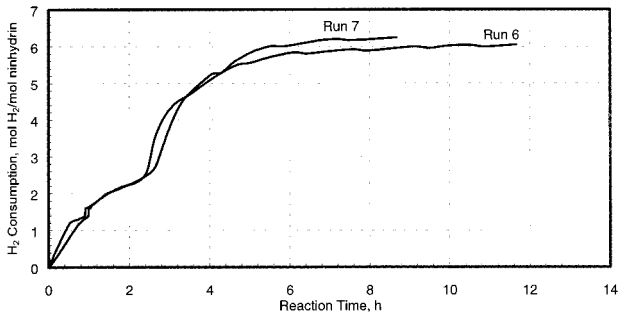


Figure 8. **Reproducibility of hydrogen consumption profiles at optimized conditions runs 6 and 7, Table 7).**

A subsequent experiment (run 7) was performed to evaluate reproducibility and to determine if the reaction could be terminated after 8 instead of 10 h. Good reproducibility can be seen based on the superimposable hydrogen consumption profiles obtained (Figure 8), including the timing of the autocatalytic process. Analysis of the reaction mixture after 8 h in run 7 indicated a nearly identical yield as that obtained with run 6 after a 12-h reaction time (Table 8). These results indicate that there was a 2-h window (8 h after the start of the reduction) for stopping the reduction without significant yield loss.

Pilot Plant Scale-Up. *Specification of Jacket Temperature Profile.* Because of the sluggish nature of the jacket temperature control system in the pilot plant reactor and the exothermic reaction occurring at early reaction time (Figure 7), cooling the jacket of the pilot plant reactor was needed to prevent batch temperature excursions. A recommended jacket temperature profile was calculated on the basis of the heat release rate measured with the RC1, Figure 7, by performing an energy balance on the pilot plant reactor contents:

$$\begin{pmatrix}\text{Rate of}\\ \text{Energy Accumulation}\end{pmatrix} = \begin{pmatrix}\text{Rate of energy}\\ \text{generation by}\\ \text{chemical reaction}\end{pmatrix} - \begin{pmatrix}\text{Rate of energy}\\ \text{lost through}\\ \text{reactor walls}\end{pmatrix} - \begin{pmatrix}\text{Rate of energy}\\ \text{loss to}\\ \text{surroundings}\end{pmatrix}$$

The rate of energy loss to the surroundings is small and can be neglected because during the first part of the reaction, the 25 °C batch temperature is very close, if not equal, to room temperature.

Thus, the rate of energy accumulation will equal the rate of energy generation by chemical reaction less the rate of energy loss to the jacket through the reactor wall:

$$mC_p \frac{dT_r}{dt} = Q_{rxn} - UA(T_r - T_j)$$

where:

m = mass of reactor contents

C_p = specific heat of reactor contents

T_r, T_j = reactor and jacket temperatures, respectively

U = overall heat transfer coefficient between reactor and batch

A = heat transfer area

A further simplification can be made if it is assumed that the rate of energy accumulation during the first part of the reaction is small (i.e., the reactor is nearly isothermal). Solving for the jacket temperature then gives:

$$T_j = T_r - \frac{Q_{rxn}}{UA}$$

The heat evolution rate Q_{rxn} and the batch temperature are determined as functions of time from calorimetric data (Figure 7). The overall heat transfer coefficient and heat transfer area corresponding to the pilot plant reactor were measured, their product being equal to 225 W/°C. Using these results, a jacket pre-cooling temperature of 10 °C was estimated to allow nearly complete heat removal due to the exothermic oxime reduction.

We emphasize that the approach outlined above is applicable strictly for small batch temperature excursions. For large-batch temperature excursions, the energy accumulation must be considered along with changes in reaction mixture and reactor wall heat conductivity which will impact the heat transfer coefficient.

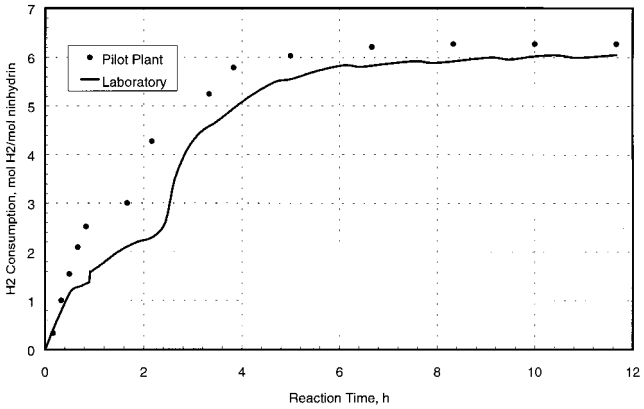


Figure 9. **Comparison of pilot plant and laboratory hydrogen consumption profiles.**

Scale-Up Results. Scale-up of Scheme 2 was performed in a 114-L reactor, representing a 100-fold scale-up from the RC1 experiments. In total, eight batches were performed to produce 17.2 kg of product. Representative results (Figure 9) indicate that good qualitative agreement was obtained between the laboratory and pilot plant hydrogen consumption profiles. A discrepancy occurred starting at about 1 h of reaction time, with the pilot plant hydrogen consumption being higher. Close examination of the batch and jacket temperature profiles revealed that after the jacket temperature was increased from 10 to 20 °C (as batch temperature control in the pilot plant was achieved by setting jacket temperature), the batch temperature underwent a temperature excursion to 30 °C. This could explain the greater hydrogen consumption in the pilot plant reactor after about 1 h of reaction due to a greater reaction rate than that in the laboratory. A more gradual jacket temperature increase would have resulted in a smaller batch temperature excursion.

After the greater H_2 consumption in the pilot plant reactor after about 1 h of reaction time, the hydrogen consumption profiles are almost parallel, indicating very good kinetic agreement between laboratory and pilot plant reactors. In particular, the autocatalytic process occurring after about 2.5 h was observed in the pilot plant, as evidenced by the presence of an inflection point in the data occurring at about 2 h. The higher hydrogen consumption in the pilot plant reactor (ca. 5%) could be due to H_2 cylinder temperature variations, as the cylinder temperature was not monitored.

Agreement in overall yield of 2-aminoindan hydrochloride between laboratory (66%) and plant (68%) was excellent, as was agreement in product purity (>97% in both cases). Thus, successful scale-up was achieved.

Conclusions

A novel synthetic route was demonstrated for producing 2-aminoindan hydrochloride, a key starting material for a drug substance, using a relatively inexpensive reactant, ninhydrin. A product isolation procedure was also devised to give the stable hydrochloride salt in good yield.

Subsequent process development work, focusing on reduction of the oxime diketone intermediate, demonstrated that the reduction could be achieved using a dry Pd/C catalyst at 20−25 °C to obtain the desired product in good yield. Using reaction calorimetry, two reaction regimes were identified: a rapid exothermic reaction involving oxime reduction, followed by a slower and much less exothermic reaction in which reduction of the diketone occurred. The delineation of these reaction regimes was used to optimize the reduction process by performing the exothermic oxime reduction at milder conditions (20 psig, 25 °C), with the slower diketone reduction carried out at higher temperature (35 °C) and pressure (40 psig) to obtain a faster reaction and reduce pilot plant time.

The optimized laboratory process was successfully scaled up 100-fold in the pilot plant, giving excellent agreement between both product yield (66% in the laboratory vs 68% in pilot plant) and product purity (>97% in all cases).

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