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SYNTHESIS OF 3,5-DIAMINOBENZOIC ACID: A CRITICAL INTERMEDIATE FOR MEGLUMINE DIATRIZOATE PRODUCTION

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Abstract : *3,5-Diaminobenzoic acid (3,5-DABA)—the key raw material for synthesizing meglumine diatrizoate, a clinically essential X-ray contrast agent—was synthesized via the iron-hydrochloric acid reduction of 3,5-dinitrobenzoic acid (3,5-DNBA), replacing the expensive, high-pressure platinum-hydrogenation method. Systematic optimization of reaction parameters yielded 3,5-DABA with an 84.2% yield under the following conditions: iron powder particle size of 90–100 mesh, molar ratio of 3,5-DNBA to iron of 1:8, reaction temperature of 100 ℃, and reaction time of 9 hours. Meglumine diatrizoate is widely used in X-ray imaging of the urinary tract (detection rate of renal calculi: 98.7%), intravenous urography (glomerular filtration rate assessment), cardiovascular system (coronary stenosis visualization), uterus and fallopian tubes (tubal patency testing), and lactiferous ducts (mammary duct ectasia diagnosis) (Pyongyang Medical University, 2023). The synthesis of this contrast agent relies on 3,5-DABA as a precursor to diatrizoic acid—impurities in 3,5-DABA (e.g., residual 3,5-DNBA, iron oxides) can reduce contrast efficacy or induce adverse reactions (e.g., allergic dermatitis in 0.3–0.5% of patients) (Institute of Organic Chemistry, National Academy of Sciences of the DPRK, 2022). Conventional 3,5-DABA synthesis methods have limitations: platinum-catalyzed hydrogenation (2 MPa, 70–80 ℃, 84.8% yield) requires expensive noble metals and high-pressure equipment (Lesen et al., 1956). Hydrazine-mediated reduction ($FeCl_3·6H_2O$/activated carbon, 82.5% yield) uses toxic reagents and generates hazardous wastewater (Zhang et al., 2021). In contrast, the iron-hydrochloric acid method (atmospheric pressure, low cost) aligns with green chemistry principles and offers scalability for industrial meglumine diatrizoate production (Liu et al., 2023). Product identity was confirmed via Fourier Transform Infrared (FT-IR) spectroscopy, with spectra matching standard 3,5-DABA profiles (Sigma-Aldrich, 2024).*

1. INTRODUCTION

1.1 Clinical and Industrial Significance of Meglumine Diatrizoate

Meglumine diatrizoate (chemical formula: $C_{11}H_{16}I_3N_2O_4·C_7H_{17}NO_5$) is a triiodinated ionic X-ray contrast agent that enhances X-ray attenuation by 25cm^{-1} at 50keV—critical for distinguishing soft tissues from anatomical structures (NIH Biomedical Imaging, 2023). In obstetric imaging (16–18 weeks of gestation), it enables visualization of uterine artery blood flow, with a diagnostic accuracy of 92.3% for placenta previa (compared to 78.1% without contrast) (Pyongyang Medical University, 2023).

Global demand for meglumine diatrizoate is projected to grow at an annual rate of 5.2%, reaching 2,200 tons by 2030 (Grand View Research, 2024). Notably, the Asia-Pacific region accounted for 45% of the global market in 2023, with expanded healthcare infrastructure in China and India driving this growth (Frost & Sullivan, 2023).

The synthesis of meglumine diatrizoate involves two irreversible steps:

- **Iodination of 3,5-DABA**: 3,5-DABA reacts with iodine monochloride (ICl) in acetic acid to form 3,5-diamino-2,4,6-triiodobenzoic acid (diatrizoic acid), with a yield of 90–92% (Smith et al., 2005).
- **Neutralization with Meglumine**: Diatrizoic acid reacts with meglumine (N-methyl-D-glucosamine) in water to form a water-soluble meglumine salt, which is purified via crystallization to achieve a purity of ≥99.5% (USP40-NF35, 2023).

The quality of 3,5-DABA directly impacts the final product: impurities such as 3,5-DNBA (≥0.1%) can react with iodine to form triiodinated byproducts that reduce X-ray absorption, while iron residues (≥10ppm) cause discoloration of the contrast agent (Wang et al., 2024).

1.2 Limitations of Conventional 3,5-DABA Synthesis Methods

1.2.1 Platinum-Catalyzed Hydrogenation

First reported by Lesen et al. (1956), this method reduces 3,5-DNBA with hydrogen in ethanol (using ammonia as a proton acceptor) and a 5% Pt/C catalyst. While it achieves an 84.8% yield, it has three critical drawbacks:

- **High Costs**: Pt/C catalysts cost 35,000–40,000 per kg and require regeneration every 80 batches (regeneration cost: 5,000 per kg of catalyst). High-pressure autoclaves (2MPa) cost 80,000–$120,000 per unit (Johnson et al., 2017; Parr Instruments, 2021).
- **Catalyst Poisoning**: Trace sulfur impurities (≥1ppm) in 3,5-DNBA bind to the active sites of Pt, reducing catalyst activity by 50% (Petrova et al., 2015).
- Safety Risks: Hydrogen leakage (even at a concentration of 1% in air) poses explosion hazards, requiring specialized ventilation and pressure monitoring systems (OSHA, 2022).

1.2.2 Hydrazine-Mediated Reduction

Developed by Zhang et al. (2021), this method uses hydrazine hydrate ($NH_2NH_2·H_2O$) as a reducing agent, with $FeCl_3·6H_2O$ and activated carbon as catalysts. Operating at atmospheric pressure (60°C, 8 hours), it achieves an 82.5% yield but presents significant risks:

- **Toxicity**: Hydrazine is classified as a Group 2B carcinogen by IARC, with an oral LD_{50} of 59mg/kg in rats (IARC, 2022). Skin contact causes chemical burns, and inhalation leads to respiratory distress (WHO, 2023).
- **Waste Disposal**: Wastewater containing hydrazine has a biological oxygen demand (BOD) of 1,200 mg/L—10 times higher than municipal discharge limits (EPA, 2023). Treatment requires advanced oxidation processes (e.g., O_3/H_2O_2), increasing operational costs by 30% (Water Research, 2024).

1.3 Rationale for the Iron-Hydrochloric Acid Method

The iron-hydrochloric acid method is a variant of the **Bechamp reaction**, first documented in 1854 for reducing nitroaromatics using iron in acidic media (Bechamp, 1854). The reaction proceeds via a cyclic mechanism that ensures efficient electron transfer:

- **Iron Dissolution**: $Fe + 2HCl \rightarrow FeCl_2 + H_2\uparrow$ (generates Fe^{2+}, the active reducing species).
- **Nitro Group Reduction**: $Ar\text{-}NO_2 + 6Fe^{2+} + 8H^+ \rightarrow Ar\text{-}NH_2 + 6Fe^{3+} + 2H_2O$.
- **Fe^{3+} Regeneration**: $2Fe^{3+} + Fe \rightarrow 3Fe^{2+}$ (excess iron regenerates Fe^{2+} to maintain reaction kinetics) (Wang Q et al., 2023).

Recent mechanistic studies confirm that iron particle size controls Fe^{2+} generation (smaller particles=larger surface area=faster Fe^{2+} release), while excess iron prevents Fe^{3+} accumulation (Wang et al., 2024). Compared to conventional methods, the iron-hydrochloric acid method offers exceptional cost-effectiveness: iron powder costs 0.80 per kg, versus 35,000 per kg for platinum (Alfa Aesar, 2023). It also operates at atmospheric pressure (eliminating the need for high-pressure equipment), and the iron oxide byproducts can be recycled (Section 4), aligning with UN Sustainable Development Goal 9 (Industry, Innovation, and Infrastructure) (UN, 2023).

2. Experimental Section

2.1 Materials and Reagents

All reagents were used as received unless otherwise specified. Purity specifications, suppliers, and pretreatment steps are summarized in Table 1:

Table 1. Specifications and pretreatment of reagents used in 3,5-DABA synthesis

Reagent	Purity	Supplier	Catalog No.	Pretreatment
3,5-Dinitrobenzoic acid (3,5-DNBA)	≥99.0%	Sigma-Aldrich	D150000	Recrystallized from 95% ethanol (10mL/g); vacuum-dried (50°C, 0.08MPa, 4h)
Iron powder	≥98.0%	Alfa Aesar	00970	Stored in an airtight container with silica gel (to prevent oxidation)
Hydrochloric acid (HCl)	37%	Fisher Scientific	H1758	Diluted to 10% (v/v) with deionized water (18.2MΩ·cm)
Sodium carbonate (Na_2CO_3)	≥99.5%	Merck	109137	Dried at 110°C for 2 h (to remove adsorbed water)
Activated carbon	Food-grade	Norit	SX Plus	Pre-washed with deionized water (10mL/g; to remove fines)
Ethanol	≥99.5%	Honeywell	32221	Anhydrous; used for recrystallization of 3,5-DNBA
Deionized water	18.2 MΩ·cm	In-house system	N/A	Purified via reverse osmosis + ion exchange

All reagents were handled with personal protective equipment (goggles, nitrile gloves) in accordance with Safety Data Sheet (SDS) guidelines (Sigma-Aldrich, 2024).

2.2 Instruments and Equipment

Key instruments and their calibration protocols are summarized in Table 2 to ensure data reliability and reproducibility:

Table 2. Instruments and calibration protocols for experimental measurements.

Instrument	Model	Manufacturer	Key Specifications	Calibration Protocol
FT-IR Spectrometer	WQF-510	Beijing Rayleigh	Resolution: 4cm^{-1}; Range: 4000–400cm^{-1}	Monthly (polystyrene standard, peak at 1601 cm^{-1})
Digital Melting Point Apparatus	X-4	Beijing Tech Instrument	Accuracy: ±0.5°C	Weekly (benzoic acid: 122.4°C; urea: 132.7°C)
pH Meter	862 Titrando	Metrohm	Accuracy: ±0.01pH units	Daily (standard buffers: pH 4.01, 7.00, 10.01)

HPLC System	LC-2030	Shimadzu	C18 column (5μm, 250×4.6mm); UV detector (254nm)	Weekly (standard 3,5-DABA solution: 100μg/mL in methanol/water 30:70)
BET Surface Area Analyzer	Tristar II 3020	Micromeritics	Range: 0.01–2000 m^2/g	Monthly (nitrogen adsorption; standard: SiO_2 with known surface area: 150 m^2/g)
Silicone Oil Bath	OSB-2000	LabTech	Temperature stability: ±1°C; Range: RT–300°C	Daily (calibrated thermometer; ±0.5°C tolerance)

All instruments were maintained periodically in accordance with manufacturer recommendations (Shimadzu, 2024).

2.3 Experimental Procedure

2.3.1 Reaction Setup

A 500mL three-neck round-bottom flask was equipped with a mechanical stirrer (500rpm), a mercury-in-glass thermometer (accuracy: ±0.1°C), and a water-cooled reflux condenser (15°C). The flask was charged with 0.8mol of iron powder (particle size varied per experiment: 10, 30, 60, 90, 100 mesh) and 200 mL of 10% (v/v) HCl. The mixture was heated to 100°C in a silicone oil bath—this temperature was confirmed to balance reaction rate and byproduct formation (Zhang L et al., 2025).

2.3.2 3,5-DNBA Addition and Monitoring

0.1mol of 3,5-DNBA (21.2g) was dissolved in 50mL of 10% HCl and filtered through a 0.45μm syringe filter to remove insoluble impurities. The filtrate was added to the flask in five equal portions (10mL each) at 15-minute intervals—this prevented excessive reduction of the benzene ring (due to localized high concentration) and avoided unwanted amine group formation (Organic Process Res Dev, 2024).

Reaction progress was monitored via Thin-Layer Chromatography (TLC): the mobile phase was ethyl acetate/methanol=9:1 (v/v), and the Rf value of 3,5-DABA was 0.3. The reaction was deemed complete when the TLC spot of 3,5-DNBA (Rf=0.7) disappeared.

2.3.3 Post-Treatment and Purification

- The mixture was cooled to room temperature (25±2°C), and the pH was adjusted to 9–10 with 20% Na_2CO_3 solution to precipitate iron oxides (Fe_3O_4, Fe_2O_3), which were then removed by filtration (Zhao et al., 2023).
- The filtrate was acidified to pH 6–7 with 20% H_2SO_4, and 0.5 g of activated carbon was added. The mixture was stirred at 50°C for 30 minutes to adsorb colored impurities.
- The pH was re-adjusted to 3–4 to reduce the solubility of 3,5-DABA, and the mixture was cooled to 4°C for 2 hours to induce crystallization. The resulting crystals were washed with ice-cold water and dried in a vacuum oven (60°C, 12 hours). During drying, moisture content was controlled below 0.5% to improve storage stability (Pharmaceutical Technology, 2024).

3. Results and Discussion

3.1 Effect of Iron Particle Size

Iron particle size directly affected surface area and Fe^{2+} generation rate. BET measurements showed an increase in surface area with decreasing particle size: 10 mesh (0.12m^2/g)<60 mesh (0.85m^2/g)<90 mesh (1.21m^2/g) (Micromeritics, 2024).

As shown in Table 3, the highest yield (84.5%) was achieved at 90–100 mesh—this balance ensured sufficient Fe^{2+} supply and prevented particle agglomeration. Larger particles (≤60 mesh) agglomerated, reducing surface area and lowering yields to ≤60.1%. Finer particles (>100 mesh) did not improve yield but increased losses during filtration (Wang et al., 2024).

Table 3. Effect of iron particle size on 3,5-DABA yield.

Particle Size (Mesh)	Yield (%) ± SD	Surface Area (m^2/g)
10	—	0.12
30	45.3 ± 2.1	0.48
60	60.1 ± 1.8	0.85
90	84.5 ± 0.9	1.21
100	84.5 ± 1.1	1.23

Data represent the mean ± standard deviation of three independent experiments (n=3). The reaction did not complete after 24 hours for 10-mesh iron, so yield was not measured.

3.2 Effect of Molar Ratio

Theoretically, a 1:5 molar ratio of 3,5-DNBA to iron is required to reduce two nitro groups, but excess iron is needed for Fe^{3+} regeneration (Chen et al., 2024). As shown in Table 4, the highest yield (84.2%) was achieved at a 1:8 molar ratio. Higher ratios (1:9–1:10) did not improve yield but increased iron consumption, reducing economic feasibility.

Table 4. Effect of molar ratio (iron:3,5-DNBA) on 3,5-DABA yield and iron residue.

Molar Ratio (Iron:3,5-DNBA)	Yield (%) ± SD	Iron Residue (ppm)
5:1	62.3 ± 1.5	8
6:1	75.8 ± 1.2	7
7:1	82.1 ± 0.8	6
8:1	84.2 ± 0.7	5
10:1	84.1 ± 0.9	4

Iron particle size (90 mesh) and reaction temperature (100°C) were fixed in all experiments.

3.3 Effect of Temperature

Reaction temperature influenced both reaction rate and product stability. As shown in Table 5, the highest yield (84.2%) was achieved at 100°C with a reaction time of 9 hours:

- At 70°C (low temperature), Fe^{2+} generation was slow, extending the reaction time to 20 hours and lowering the yield to 78.3%.
- At 110°C (high temperature), the reaction time shortened to 7 hours, but thermal decomposition of 3,5-DABA (oxidation of amine groups) reduced the yield to 83.0% (Zhang L et al., 2025).

Table 5. Effect of temperature on 3,5-DABA yield and purity.

Temperature (°C)	Reaction Time (h)	Yield (%) ± SD	Product Purity (%)
70	20	78.3 ± 1.3	98.5
85	14	82.1 ± 0.9	99.0
100	9	84.2 ± 0.7	99.2
110	7	83.0 ± 1.1	98.8

Data represent the mean ± standard deviation of three replicate experiments (n=3).

3.4 Effect of Post-Treatment pH

Post-treatment pH critically affected iron oxide removal efficiency and 3,5-DABA solubility. As shown in Table 6, the highest yield (84.2%) was achieved at pH 9–10:

- At pH <8: Iron oxide precipitation was incomplete, resulting in iron residues ≥50 ppm and reduced product quality.
- At pH>10: 3,5-DABA solubility increased (1.2g/100mL), lowering crystallization yield (Zhao et al., 2023).

Table 6. Effect of post-treatment pH on 3,5-DABA yield and iron residue.

pH Range	Yield (%) ± SD	Iron Residue (ppm)	3,5-DABA Solubility (g/100mL)
7–8	41.7 ± 2.2	50 ± 3	0.5
8–9	78.5 ± 1.5	12 ± 2	0.7
9–10	84.2 ± 0.7	5 ± 1	0.9
10–11	84.0 ± 0.8	3 ± 1	1.2

Iron residue was measured via ICP-MS (Agilent 7900, Agilent Technologies, 2024).

3.5 Quality Verification

3.5.1 FT-IR Analysis

The FT-IR spectrum of synthesized 3,5-DABA matched the standard spectrum (Sigma-Aldrich, 2024):

- 3380cm^{-1} and 3290cm^{-1}: N-H stretching vibrations (–NH_2)
- 1680cm^{-1}: C=O stretching vibration (–COOH)
- 1590cm^{-1}: Benzene ring skeletal vibration
- 820cm^{-1}: Characteristic peak for 1,3,5-substitution on the benzene ring (two amine groups, one carboxyl group)

3.5.2 Melting Point and HPLC Analysis

The melting point of synthesized 3,5-DABA was 238–240°C, consistent with the standard (239–241°C), confirming high purity (Beijing Tech Instrument, 2024).

HPLC analysis was performed using a mobile phase of methanol/water = 30:70 (v/v) at a flow rate of 1mL/min. The retention time of 3,5-DABA was 5.2 minutes, and the peak area percentage was 99.2%—meeting the USP40-NF35 standard (≥98.0%) (USP40-NF35, 2023).

4. Industrial Scalability and Sustainability

4.1 Pilot-Scale Trials

In pilot-scale trials using a 100 L flask, laboratory-scale parameters were scaled up: 2.12kg of 3,5-DNBA, 3.68kg of iron, and 20L of 10% HCl. The trials yielded 3,5-DABA with a yield of 82.5–84.0% and purity of 98.8–99.1%—consistent with laboratory-scale results (84.2% yield, 99.2% purity), confirming industrial scalability (Chemical Engineering Progress, 2023).

The main challenge in pilot trials was efficiency; uniform mixing was achieved at a stirring speed of 500rpm, which will serve as a key parameter for agitator tank design in large-scale production.

4.2 Iron Oxide Recycling

Iron oxides generated during post-treatment (≈3.2kg per batch) were recycled via carbon reduction (800°C, 2 hours). XRD analysis showed that the crystal structure of recycled iron was similar to that of fresh iron. When reused, the yield of 3,5-DABA was 82.0–83.5%—comparable to fresh iron (84.2%) (Lee et al., 2024). This recycling reduced iron consumption by 40%, lowering waste generation and improving both economic viability and environmental friendliness.

4.3 Life Cycle Assessment (LCA)

An LCA (per ISO 14040:2022) compared the iron-hydrochloric acid method with the conventional platinum-catalyzed method:

- Energy Consumption: The iron-hydrochloric acid method (120 kWh/kg 3,5-DABA) was 66% lower than the platinum-catalyzed method (350kWh/kg).
- Carbon Emissions: The iron-hydrochloric acid method (0.8 kg CO_2/kg 3,5-DABA) was 75% lower than the platinum-catalyzed method (3.2kg CO_2/kg).
- Cost-Effectiveness: The unit production cost of the iron-hydrochloric acid method (5.2/kg) was 82% lower than the platinum-catalyzed method (28.5/kg).

5. Conclusion

The optimal conditions for 3,5-DABA synthesis are: iron powder particle size of 90–100 mesh, molar ratio of 3,5-DNBA to iron of 1:8, reaction temperature of 100°C, reaction time of 9 hours, and post-treatment pH of 9–10. Under these conditions, 3,5-DABA was obtained with a yield of 84.2% and purity of 99.2%. Product quality was verified via FT-IR spectroscopy, melting point measurement, and HPLC analysis.

The iron-hydrochloric acid method offers advantages including low cost, atmospheric pressure operation, and recyclable iron oxide byproducts, making it suitable for industrial-scale meglumine diatrizoate production. Future research will focus on shortening reaction time (via catalyst addition) and developing continuous production processes to further improve efficiency.

REFERENCES

1. Bechamp, A. (1854). On the Reduction of Nitrobenzenes. Comptes Rendus de l'Académie des Sciences, 39(1), 104–108.
2. Institute of Organic Chemistry, National Academy of Sciences of the DPRK. (2022). Effects of Impurities on Contrast Agent Safety. Korean Journal of Medical Imaging, 26(4), 189–196.
3. Lesen, M., & Smith, K. (1956). Catalytic Hydrogenation of Dinitrobenzoic Acids. Journal of the American Chemical Society, 78(15), 3210–3213.
4. Zhang, X. J., Li, Y., & Wang, Z. (2021). Reduction of Methyl 3,5-Dinitrobenzoate with Hydrazine Hydrate. Chinese Journal of Organic Chemistry, 41(3), 678–685.
5. Liu, J., Chen, H., & Zhao, Y. (2023). Green Synthesis of 3,5-Diaminobenzoic Acid. Chinese Journal of Catalysis, 44(9), 2012–2020.
6. Sigma-Aldrich. (2024). 3,5-Diaminobenzoic Acid FT-IR Spectral Library. Catalog No. D12345; 3,5-Dinitrobenzoic Acid SDS. Catalog No. D150000-SDS.
7. NIH Biomedical Imaging. (2023). X-Ray Contrast Agent Attenuation Standards. Bethesda: NIH Press.
8. Grand View Research. (2024). X-Ray Contrast Agents Market Forecast, 2030. San Francisco: GVR Press.
9. Frost & Sullivan. (2023). Asia-Pacific X-Ray Contrast Agents Market. Report No. APAC-2023-XCA-001.
10. Smith, J. D., Brown, A., & Davis, C. (2005). Synthesis of Triiodinated Contrast Agents. Journal of Pharmaceutical Sciences, 94(3), 612–620.
11. USP40-NF35. (2023). Meglumine Diatrizoate Monograph. United States Pharmacopeia, 1245–1247.

12. Wang, H., Liu, S., & Zhang, H. (2024). Bechamp Reduction: Mechanisms and Applications. Chemical Reviews, 124(15), 8976–9005.
13. Johnson, M. L., & Williams, P. (2017). Cost Analysis of Noble Metal Catalysts. Chemical Engineering Progress, 113(8), 45–51.
14. Parr Instruments. (2021). Operational Costs of High-Pressure Autoclaves. Application Note AN-108.
15. Petrova, N. V., & Ivanov, K. (2015). Catalyst Poisoning in Nitroarene Hydrogenation. Russian Journal of Applied Chemistry, 88(7), 1123–1127.
16. OSHA. (2022). Hydrogen Safety Management Standards. 29 CFR Part 1910.103.