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Original Research Article

Optimization and Process Scale-up for the Synthesis of Pharmaceutical-Grade *N*-Acetyl-DL-Leucine from L-Leucine

Mai Van Phong [1], Pham Nguyen Vu[2], Vu Duc Thanh[3]

[1]*Polytechnic College of Engineering and Technology,Viet Nam.*

[2]*Hanoi Amsterdam High School for the Gifted, Viet Nam.*

[3]*High School for Gifted, Hanoi National University of Education, Viet Nam.*

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Abstract - N-Acetyl-DL-leucine is a well-established active pharmaceutical ingredient widely prescribed for the symptomatic treatment of vestibular vertigo. However, its industrial supply in developing markets still relies heavily on imports due to a lack of optimized, large-scale domestic manufacturing processes. Herein, we report an eco-friendly, highly reproducible, and cost-effective synthetic process for pharmaceutical-grade N-acetyl-DL-leucine from readily available L-leucine, scaled up to 1 kg/batch. The procedure comprises two main steps: N-acylation of L-leucine with acetic anhydride (Ac_2O) in an aqueous sodium hydroxide solution, followed by catalytic thermal racemization. Key operational parameters were systematically investigated to optimize the overall process. The ideal acylation conditions were achieved at 20--45°C with a molar ratio of Ac_2O:L-leucine = 2.1: 1, and product isolation was optimal by acidification to pH = 3. Subsequent racemization in an aqueous environment proceeded completely at 90°C for 5 hours using a 1:1 molar ratio of Ac_2O to N-acetyl-L-leucine. Scale-up trials executed at 100 g/batch and 1 kg/batch demonstrated remarkable consistency, delivering an overall yield of 87.28% with a chemical assay purity of 98.1% at the 1 kg/batch level, as determined by HPLC and acid-base titration. The chemical structure of the synthesized compound was unambiguously validated by IR, ESI-MS, ^{1}H-NMR, and ^{13}C-NMR spectroscopies. Complete racemization was confirmed by an optical rotation value of $[\alpha]_D^{20} = 0°$. Overall, this robust, water-based synthetic route avoids hazardous organic solvents and offers a practical, industrial-ready solution for domestic N-acetyl-DL-leucine production.

Keywords - *Acylation, API synthesis, L-Leucine, N-Acetyl-DL-leucine, Process Scale-up, Racemization.*

I. INTRODUCTION

Vertigo is a common symptom of vestibular disorientation that is defined by the sensation of motion or the illusion of spinning, usually along with autonomic neurovegetative signs, nystagmus and gait instability [1]. Epidemiological studies show that vertigo occurs in 20–30% of the general population at some time in their lives, with an annual incidence rate of around 11% and a higher incidence in persons over 75 years of age [2]. *N*-acetyl-DL-leucine (NAL), is a prominent active pharmaceutical ingredient (API) used in the symptomatic treatment of acute and chronic vestibular vertigo, and is widely marketed in Europe (e.g. Tanganil) and elsewhere in the world. Mechanistically, NAL stabilizes vestibular excitability by restoring membrane potential polarization and modulating the interaction of membrane phospholipids in damaged vestibular neurons that accelerate central vestibular compensation without affecting physiological neuronal functions [4, 5].

Although NAL has a high therapeutic value, most of the domestic supply in many developing markets such as Vietnam is based on imported active raw materials [6]. The existing academic literature and the patents are mainly concerned with laboratory-scale synthesis of small quantities from 1 g to 10 g per batch [7]. In addition, traditional synthetic methods have some significant industrial scale-up problems [8]. The use of gaseous

reagents, like ketene, is prone to operational risks and low yields of desired products [9]. However, alternative approaches using organometallic catalysts (e.g., cobalt, rhodium, palladium) or volatile hazardous solvents (such as toluene) present economic and environmental challenges [10, 11]. Continuous-flow microreactor technology is highly efficient but involves complex non-standard equipment, making direct transfer of the technology in a standard batch industrial reactor difficult [12].

To bridge the gap between laboratory synthesis and industrial API manufacturing, developing a green, scalable, and cost-effective process using standard batch equipment is essential [13]. This study presents an optimized two-step batch synthesis of pharmaceutical-grade *N*-acetyl-DL-leucine from readily available L-leucine [14]. The process utilizes an aqueous medium, avoiding harmful organic solvents [15]. Key reaction parameters including solvent volume, operating temperatures, crystallization pH, and reagent stoichiometric ratios were systematically investigated to overcome exothermicity and volume limitations [16]. The synthetic route was successfully validated and scaled up to 100 g/batch and 1 kg/batch levels [17]. The synthesized product was thoroughly characterized by spectroscopic methods (IR, ESI-MS, ^{1}H-NMR, and ^{13}C-NMR), polarimetry, and verified against full quality control standards [18].

II. MATERIALS AND METHODS

A. Reagents and Equipment

All starting materials, reagents, and solvents used in this study were of analytical reagent (AR) grade or pharmaceutical grade and were utilized without further purification [1]. L-Leucine (≥ 98.5%, Batch No. 20220323) was purchased from Hebei Changhao (China) [1]. Acetic anhydride (Ac_2O, AR), sodium hydroxide ($NaOH$, AR), hydrochloric acid (HCl 37%, AR), acetic acid ($AcOH$ 99.5%, AR), succinic anhydride (AR), phthalic anhydride (AR), sodium acetate (CH_3COONa, AR), and ninhydrin (AR) were supplied by Sinopharm Chemical Reagent Co., Ltd. (China) [1]. High-performance liquid chromatography (HPLC)-grade acetonitrile and sodium heptanesulfonate were purchased from Merck (Germany) [1]. Distilled water complying with Vietnamese Pharmacopoeia V standards was generated in-house [1].

Melting points were determined using an EZ-Melt automated melting point apparatus (Stanford Research Systems, USA) [1]. Specific optical rotations $[\alpha]_D^{20}$ were recorded on an AK Krüss P1000-LED polarimeter (Germany) with a 2-dm cell path length in ethanol at 20°C [1]. Thin-layer chromatography (TLC) was conducted on Silica Gel 60 F_{254} aluminum sheets (Merck, Germany), visualized by spraying with 0.2% ninhydrin solution in ethanol followed by thermal development [1]. Infrared (IR) spectra were recorded on a Shimadzu FTIR Affinity-1S spectrometer (Japan) using KBr pellets (400--4000 cm^{-1}, resolution 4 cm^{-1}) [1]. Electrospray ionization mass spectra (ESI-MS) were acquired on an LC-MSD-Trap-SL system (Agilent Technologies, USA) [1]. Nuclear magnetic resonance (^{1}H-NMR at 500 MHz or 600 MHz, and ^{13}C-NMR at 125 MHz or 150 MHz) spectra were recorded on a Bruker Avance spectrometer (Germany) in DMSO-d_6 with tetramethylsilane (TMS) as an internal standard [1]. Process scale-up at the 1 kg/batch level was carried out in a 5-L jacketing glass reactor system (Chemglass, USA) equipped with an overhead mechanical stirrer and temperature control unit [1].

B. Optimization of N-Acetyl-L-Leucine Synthesis (Acylation Step)

In a typical optimization batch, L-leucine (10.00 g, 76.23 mmol) was suspended in an aqueous $NaOH$ solution (4 M, 300.00 mmol) in a three-necked round-bottom flask under magnetic stirring [1]. The reaction mixture was cooled to 20--25°C until complete dissolution [1]. Acetic anhydride (15 mL, 158.98 mmol) was added dropwise into the solution while maintaining the internal temperature below 45°C to control exothermic heat generation [1]. Reaction progress was monitored by TLC using an *n*-butanol:acetic acid:water (9: 2.5: 2.5 v/v/v) solvent system [1]. Upon reaction completion (3 hours), the mixture was acidified using concentrated HCl to precipitate *N*-acetyl-L-leucine [1]. To optimize process economics and reduce total liquid volume for large-scale production, several key variables were systematically evaluated: water volume (35, 20, and 15 mL per 10 g of L-leucine) [1], reaction temperature (20--30°C, 30--40°C, 40--50°C, and 50--55°C) [1], and precipitation pH (pH 2, 3, 4, and 5) [1]. The isolated precipitate was filtered, washed with cold distilled water until chloride-free (silver nitrate test negative), and collected directly for the subsequent racemization step [1].

C. Optimization of N-Acetyl-DL-Leucine Synthesis (Racemization Step)

N-Acetyl-L-leucine (10.00 g, 58.7 mmol) was dissolved in an aqueous solution containing $NaOH$ (2.32 g, 58.0 mmol) and distilled water (100 mL) [1]. The solution was heated to 90°C, followed by the slow addition of acetic anhydride as a racemization catalyst [1]. The mixture was stirred at 90°C for 3--5 hours [1]. After cooling to room temperature, the mixture was acidified with concentrated HCl to pH = 3 to induce crystallization [1]. The precipitate was filtered, washed thoroughly with cold water, and dried at 60°C for 3 hours to obtain crude N-acetyl-DL-leucine [1].

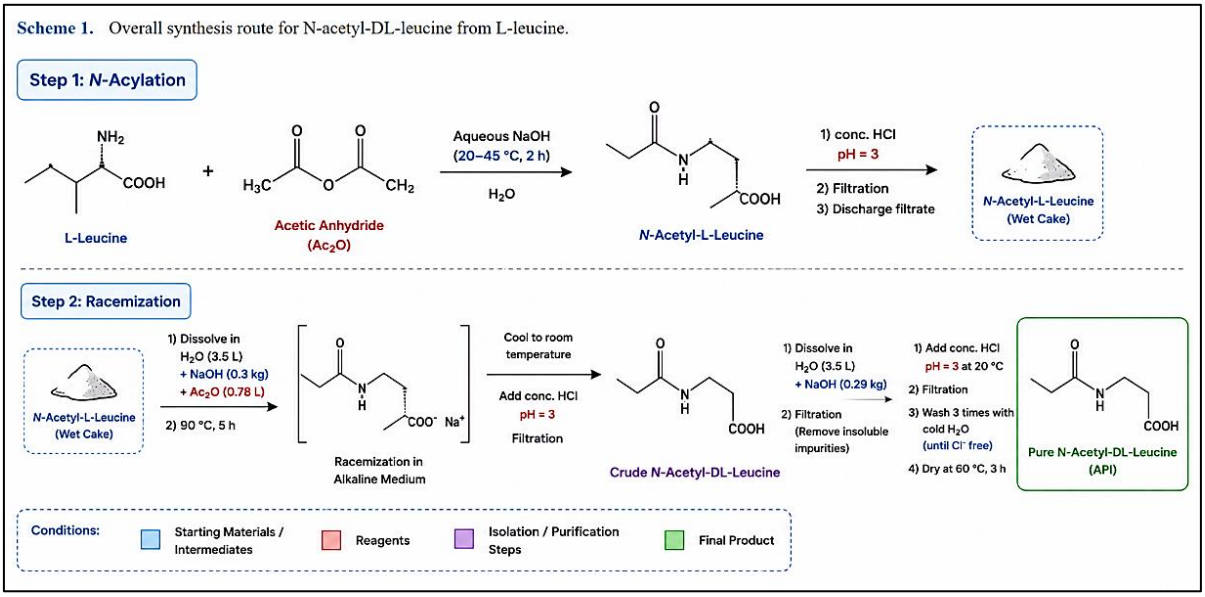
The racemization efficiency was optimized by investigating: molar ratio of Ac_2O to N-acetyl-L-leucine (2.6: 1 down to 0.10: 1) [1], water volume (50, 40, 30, and 20 mL per 10 g of N-acetyl-L-leucine) [1], and alternative catalytic systems ($NaOH$ alone, $AcOH + NaOH$, CH_3COONa combinations, succinic anhydride, and phthalic anhydride) [1].

D. Product Purification Procedure

Crude N-acetyl-DL-leucine was purified by alkaline redissolution followed by controlled reprecipitation [1]. Briefly, crude N-acetyl-DL-leucine was dissolved in an aqueous solution of $NaOH$ (2.32 g in 30 mL water per 10 g crude) [1]. The solution was filtered to remove insoluble impurities [1]. The clear filtrate was slowly acidified with concentrated HCl to pH = 3 at 20 ± 2°C under constant stirring [1]. The resulting white crystalline precipitate was collected by filtration, washed three times with cold distilled water until silver nitrate negative for chloride ions, and dried at 60°C for 3 hours to yield pure pharmaceutical-grade N-acetyl-DL-leucine [1].

E. Scaled-up Synthesis at 100 g/batch and 1 kg/batch

The general two-step reaction pathway for the synthesis of N-acetyl-DL-leucine from L-leucine is illustrated in Scheme 1.



Scheme 1. Reaction pathway for the synthesis of N-acetyl-DL-leucine from L-leucine

1) **Scale-up at 100 g/batch**: Distilled water (200 mL), NaOH (100 g, 2.50 mol), and L-leucine (100 g, 0.76 mol) were added to a 1-L reaction vessel [1]. Acetic anhydride (150 mL, 1.59 mol) was added dropwise while maintaining the temperature below 45°C, followed by stirring for 3 hours [1]. Concentrated HCl (180 mL) was added to adjust the pH to 3 [1]. The filtered precipitate was redissolved in water (350 mL) containing NaOH (30 g), treated with acetic anhydride (78 mL, 1.08 eq), and stirred at 90°C for 5 hours [1]. Crystallization was induced at pH = 3 using HCl (59 mL) [1]. The crude product was purified by redissolving in aqueous NaOH (29 g in 350 mL water), filtering, re-acidifying to pH = 3 with HCl (52 mL), washing, and drying at 60°C [1].
2) **Scale-up at 1 kg/batch**: In a 5-L glass reactor equipped with a mechanical stirrer (150 rpm), L-leucine (1.0 kg, 7.62 mol) was dissolved in 2.0 L of water containing NaOH (1.0 kg, 25.0 mol) [1]. Acetic

anhydride (1.5 L, 15.87 mol) was added dropwise with external water cooling to maintain the temperature within 20--45°C [1]. After 2 hours of reaction, concentrated HCl (1.8 L) was added to adjust the mixture to pH = 3 [1]. The collected wet cake of N-acetyl-L-leucine was directly suspended in 3.5 L of water containing NaOH (0.3 kg), followed by addition of acetic anhydride (0.78 L) [1]. The mixture was stirred at 90°C for 5 hours (7.5 hours under modified cooling constraint at 60°C) [1]. Upon cooling, acidification to pH = 3 with HCl (0.59 L) yielded crude N-acetyl-DL-leucine [1]. Re-crystallization was performed by dissolving in aqueous NaOH (0.29 kg in 3.5 L water), filtering insoluble matter, reprecipitating at pH = 3 with HCl (0.52 L), washing with water until chloride-free, and drying at 60°C to constant weight [1].

The complete operational flow diagram for the industrial 1 kg/batch process is outlined in Figure 1.

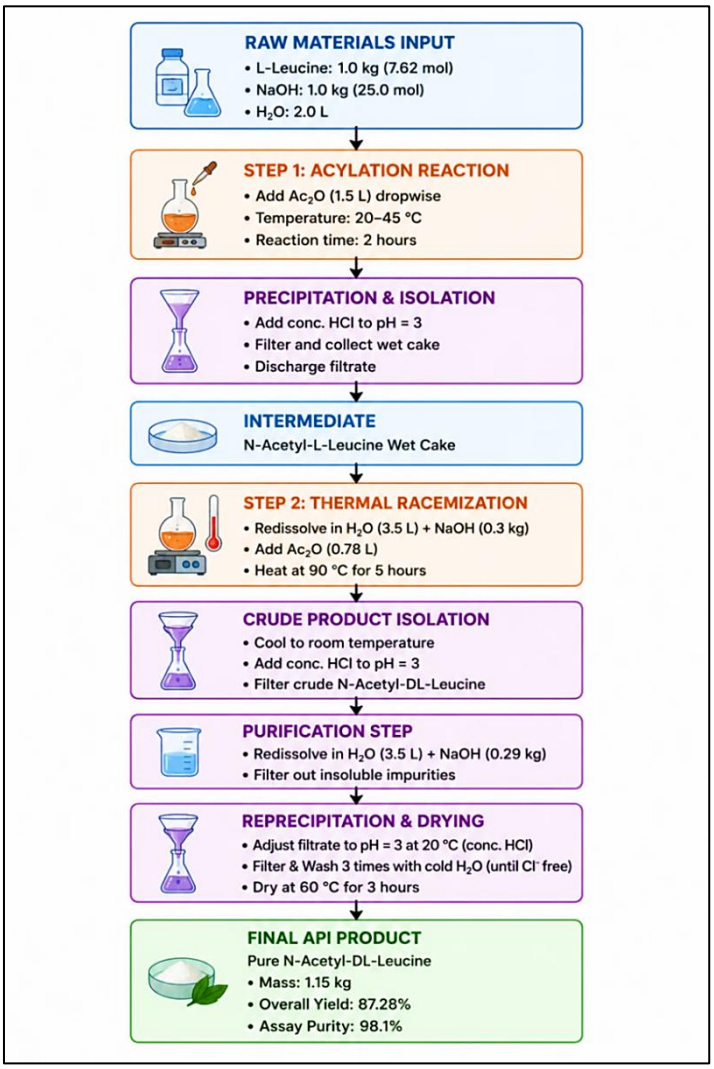


Figure 1. Operational flow process for 1 kg/batch synthesis of N-acetyl-DL-leucine

F. Analytical and Quality Control Specifications

Quality control parameters and acceptance criteria for pharmaceutical-grade N-acetyl-DL-leucine are detailed in Table 1 [1].

Table 1. In-house Quality Standards and Test Specifications for N-Acetyl-DL-Leucine

Parameter / Quality Test	Acceptance Criteria / Specification	Method / Equipment
Appearance	White crystalline powder or colorless crystals	Visual inspection

Identification (IR)	Conforms to standard reference spectrum	FTIR (KBr pellet)
Identification (HPLC)	Retention time matches standard reference peak	HPLC-UV (205 nm)
Melting Point	157.5--161.0°C	Automated EZ-Melt
Specific Optical Rotation	$-0.2°$ to $+0.2°$ ($c = 1\%$ in EtOH)	Polarimeter (20°C)
Loss on Drying	$\leq 1.0\%$	Vacuum drying (70°C, 3 h)
Heavy Metals	≤ 20 ppm	Pharmacopoeial Method 1
Sulfated Ash	$\leq 0.1\%$	Pharmacopoeial Method 2
Chloride Content	$\leq 0.04\%$	Silver nitrate turbidity
Related Impurities	Any individual peak $\leq 0.5\%$; Total $\leq 1.0\%$	HPLC-UV
Assay Content	98.0%--102.0% (dried basis)	Acid-base titration / HPLC

1) **Acid-Base Titration Method**: Accurately weighed sample (0.1735 g) was dissolved in 10 mL of 96% ethanol, and 0.05 mL of phenolphthalein indicator was added [1]. The solution was titrated with 0.1 N NaOH (standardized against 0.1 N oxalic acid, correction factor K = 0.9090) until a light pink color persisted [1]. Each mL of 0.1 N NaOH corresponds to 17.321 mg of $C_8H_{15}NO_3$ [1].
2) **HPLC Assay and Purity Method**: Performed according to Vietnamese Pharmacopoeia V standards [1]. Analyses were executed on a C18 column (250 mm × 4.6 mm, 5 µm) maintained at ambient temperature [1]. The mobile phase consisted of phosphate buffer (pH = 2.5, prepared from 6.8 g KH_2PO_4 and 0.5 g sodium heptanesulfonate in 1000 mL water adjusted with H_3PO_4) and acetonitrile (75: 25 v/v) at a flow rate of 1.0 mL/min [1]. UV detection was set at 205 nm, with an injection volume of 20 µL [1]. Sample solutions (1.0 mg/mL) were prepared in the mobile phase [1]. Peak areas of standard and sample solutions were compared to calculate API purity [1].

III. RESULTS AND DISCUSSION

A. Optimization of N-Acylation of L-Leucine

The *N*-acylation of L-leucine to form *N*-acetyl-L-leucine proceeds via nucleophilic attack of the unprotonated amino group ($-NH_2$) on the carbonyl carbon of acetic anhydride, followed by proton abstraction and elimination of acetic acid [1]. Aqueous sodium hydroxide converts the amino acid into its nucleophilic sodium L-leucinate form while neutralizing liberated acetic acid [1]. To overcome volume constraints for scale-up, the volume of water was reduced from 75 mL down to 20 mL per 10.00 g of L-leucine without compromising dissolution or yield [1]. Further reduction to 15 mL led to incomplete dissolution and residual unreacted starting material ($R_f = 0.61$ on TLC; broad melting range 183.1--250.0°C), as detailed in Table 2 [1].

Table 2. Optimization of Water Volume in N-Acetyl-L-Leucine Synthesis (10.00 g L-Leucine)

Exp.	L-Leucine (g)	H2O Volume (mL)	Melting Point (°C)	TLC Observation
1	10.00	35	186.6--187.8	Single spot (complete reaction)
2	10.00	20	187.1--189.2	Single spot (complete reaction)
3	10.00	15	183.1--250.0	Residual spot at $R_f = 0.61$

Temperature control during Ac_2O addition is critical because the reaction is strongly exothermic [1]. As shown in Table 3, maintaining the reaction temperature below 45°C provided high yields (95.9%--96.8%) [1]. Exceeding 50°C caused a yield drop to 90.1%, accompanied by potential formation of N,N-diacetylated side products [1].

Table 3. Effect of Reaction Temperature on N-Acetyl-L-Leucine Yield

Exp.	Temperature (⁰C)	Product Mass (g)	Yield (%)	Melting Point (⁰C)
1	**20--30**	12.78	96.8	**186.3--189.1**
2	**30--40**	12.74	96.5	**183.4--186.0**
3	**40--50**	12.66	95.9	**183.7--187.3**
4	**50--55**	11.90	90.1	**184.5--186.7**

Precipitation of N-acetyl-L-leucine relies on converting sodium N-acetyl-L-leucinate into its insoluble free acid form [1]. Acidification to pH = 3 with concentrated HCl achieved a 90.9% precipitation efficiency [1]. Decreasing the pH to 2 required excessive acid without increasing product yield (91.1%), whereas higher pH values (pH = 4--5) sharply reduced recovery (48.2%--23.6%), as shown in Table 4 [1].

Table 4. Effect of Acidification pH on N-Acetyl-L-Leucine Precipitation Efficiency

Exp.	L-Leucine Equivalent (g)	Target pH	Precipitate Mass (g)	Recovery Yield (%)
1	2.50	2	4.01	91.1
2	2.50	3	4.00	90.9
3	2.50	4	2.12	48.2
4	2.50	5	1.04	23.6

B. Optimization of Thermal Racemization

Racemization of $\boldsymbol{N}$-acetyl-L-leucine is driven by oxazolinone (azlactone) intermediate formation in the presence of acetic anhydride, enabling planar enolization and loss of optical activity [1]. Systematic variation of the $\boldsymbol{Ac_2O}$:$\boldsymbol{N}$-acetyl-L-leucine molar ratio revealed that a **1**:**1** stoichiometric ratio at **90**°C for **5** hours achieved complete racemization ($[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}} = \boldsymbol{0}°$, m.p. **159.0--161.4**°C) [1]. Lower molar ratios (**0.10**:**1** to **0.75**:**1**) resulted in incomplete racemization with residual negative optical rotation ($[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}} = \boldsymbol{-22.7}°$ to $\boldsymbol{-10.6}°$), as summarized in Table 5 [1].

Table 5. Influence of Ac_2O Molar Ratio on Thermal Racemization (5 h at 90°C)

Exp.	Ac2O Volume (mL)	Ac2O:NAL Molar Ratio	Melting Point (⁰C)	Optical Rotation [α]D20
1	0.06	**0.10:1**	**182.1--184.8**	**−22.7°**
2	0.14	**0.25:1**	**175.1--181.5**	**−18.1°**
3	0.28	**0.50:1**	**159.4--171.1**	**−10.3°**
4	0.4	**0.75:1**	**161.4--176.2**	**−10.6°**
5	0.55	**1.00:1**	**159.0--161.4**	**0°**
6	0.61	**1.10:1**	**158.3--160.1**	**0°**

Water volume during racemization was optimized to **30** mL per **10.00** g of $\boldsymbol{N}$-acetyl-L-leucine [1]. Reducing water to **20** mL required heating to **60**°C to achieve initial dissolution and caused premature sodium salt crystallization during handling, leading to incomplete racemization ($[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}} = \boldsymbol{-0.8}°$) [1]. Attempts to substitute $\boldsymbol{Ac_2O}$ with inorganic/organic bases ($\boldsymbol{NaOH}$, $\boldsymbol{CH_3COONa}$) or cyclic anhydrides (succinic or phthalic anhydride) failed to induce racemization ($[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}} = \boldsymbol{-21.7}°$ to $\boldsymbol{-23.0}°$) [1]. This confirms that oxazolinone formation facilitated specifically by $\boldsymbol{Ac_2O}$ is essential for alpha-carbon deprotonation [1]. Purification of crude $\boldsymbol{N}$-acetyl-

DL-leucine by dissolution in aqueous $\boldsymbol{NaOH}$, filtration of insoluble matter, and reprecipitation at pH $= \mathbf{3}$ yielded pure product ($\mathbf{88.8}$% recovery yield) with a sharp melting point ($\mathbf{159.4}$--$\mathbf{160.5}$°C, $\boldsymbol{\Delta T} = \mathbf{1.1}$°C) and zero optical rotation [1].

C. Scale-Up Synthesis and Reproducibility

Using the optimized parameters, scale-up syntheses were evaluated at **100** g/batch (3 consecutive runs) and **1** kg/batch levels [1]. As presented in Table 6, the **100** g batches showed excellent consistency, achieving an average overall yield of $\mathbf{87.13}$% and an API assay purity of $\mathbf{98.5}$% [1]. At the **1** kg/batch scale performed in a 5-L glass reactor, the process delivered $\mathbf{1.15}$ kg of pharmaceutical-grade $\boldsymbol{N}$-acetyl-DL-leucine, corresponding to an overall yield of $\mathbf{87.28}$% [1]. The product exhibited a sharp melting point ($\mathbf{156.7}$--$\mathbf{159.2}$°C), zero optical rotation ($[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}} = \mathbf{0}°$), and an assay purity of $\mathbf{98.1}$% [1].

Table 6. Reproducibility and Scale-Up Results for N-Acetyl-DL-Leucine Synthesis

Batch Scale	Run No.	Input L-Leucine	Output Product	Overall Yield (%)	Melting Point (∘C)	Assay Content (%)
10 g/batch	Average ($\boldsymbol{n} = \mathbf{3}$)	$\mathbf{10.00}$ g	$\mathbf{11.37}$ g	87.15	$\mathbf{158.9}$--$\mathbf{160.1}$	99.37
100 g/batch	Batch 1	$\mathbf{100.0}$ g	$\mathbf{114.63}$ g	86.81	$\mathbf{157.6}$--$\mathbf{160.0}$	98.6
	Batch 2	$\mathbf{100.0}$ g	$\mathbf{115.70}$ g	87.62	$\mathbf{158.0}$--$\mathbf{160.3}$	98.4
	Batch 3	$\mathbf{100.0}$ g	$\mathbf{114.81}$ g	86.95	$\mathbf{157.9}$--$\mathbf{160.5}$	98.6
	Average	$\mathbf{100.0}$ g	$\mathbf{115.05}$ g	87.13	—	98.5
1 kg/batch	Batch 1	$\mathbf{1.0}$ kg	$\mathbf{1.15}$ kg	87.28	$\mathbf{156.7}$--$\mathbf{159.2}$	98.1

D. Pharmacopoeial Quality Evaluation

Three independent batches synthesized at the **10** g scale (Certificates of Analysis Nos. 24N-12, 24N-13, 24N-14 issued by the Institute of Drug Quality Control) and the **1** kg batch were evaluated against the established in-house quality standards [1]. All samples met pharmacopoeial specifications [1]. Loss on drying was $\leq \mathbf{0.3}$% (limit $\leq \mathbf{1.0}$%), heavy metals were within limits ($\leq \mathbf{20}$ ppm), sulfated ash was $\mathbf{0.1}$% (limit $\leq \mathbf{0.1}$%), and chloride content was $\leq \mathbf{0.04}$% [1]. Total related impurities by HPLC were below $\mathbf{1.0}$% [1]. Acid-base titration confirmed API assay content between $\mathbf{98.0}$%--$\mathbf{100.6}$% across all tested batches [1].

E. Structural Elucidation and Spectroscopic Characterization

The molecular structure of synthesized N-acetyl-DL-leucine ($C_8H_{15}NO_3$, MW 173.21 g/mol) was verified by IR, ESI-MS, ^{1}H-NMR, and ^{13}C-NMR spectroscopies [1].

1. **FTIR Spectrum**: Key characteristic absorption bands (ν_{max}, cm^{-1}) included: 3329 cm^{-1} (N--H amide stretch), 3092 cm^{-1} (O--H carboxylic acid stretch), 2959 cm^{-1} and 2871 cm^{-1} (sp^3 C--H aliphatic stretch), 1697 cm^{-1} (C=O carboxylic acid stretch), 1613 cm^{-1} (C=O secondary amide stretch), and 1238 cm^{-1} (C--O stretch) [1].
2. **Mass Spectrum (ESI-MS)**: Mass spectrometry in negative mode exhibited a prominent pseudo-molecular ion peak at m/z 171.9 $[M-H]^-$, corresponding to $C_8H_{14}NO_3^-$ [1]. Positive mode displayed a sodium adduct ion at m/z 195.8 $[M+Na]^+$, matching the theoretical molecular weight of 173.21 g/mol [1].
3. **^{1}H-NMR Spectrum (500 MHz, DMSO-d_6, δ ppm)**: δ 12.46 (s, 1H, −COOH); 8.08 (d, J = 7.93 Hz, 1H, −NH −); 4.21--4.17 (m, 1H,H-2, −CH −); 1.83 (s, 3H,H-2', $-COCH_3$); 1.68--1.55 (m, 1H,H-4, −CH −); 1.55--1.40 (m, 2H,H-3, $-CH_2$ −); 0.89 (d, J = 6.6 Hz, 6H,H-5, H-1'', 2 × $-CH_3$) [1]. The absence of free $-NH_2$ proton signals and the presence of singlet at 1.83 ppm ($-COCH_3$) confirmed complete N-acetylation [1].
4. **^{13}C-NMR Spectrum (125 MHz, DMSO-d_6, δ ppm)**: All eight carbon atoms were accounted for: δ 174.75 (C-1, −COOH); 169.73 (C-1', −C=O amide); 50.64 (C-2, −CH −); 40.25 (C-3, $-CH_2$ −); 24.78 (C-4, −CH −); 23.31 (C-2', $-CH_3$ acetyl); 22.79 (C-1'', $-CH_3$); 21.77 (C-5, $-CH_3$) [1].

F. Comparative Evaluation with Existing Synthetic Routes

To further assess the novelty, greenness and practicality of the developed protocol, our two-step aqueous batch process was systematically compared to the previously reported synthetic protocol for N-acetyl-DL-leucine (NAL) and related amino acid derivative APIs. The classical methods of NAL production described by Cahill and Burton [9] and Donghai [14] involved using gaseous reagents (e.g., ketene) or toxic organic solvents (e.g., toluene and pyridine) to promote acylation and racemization. Although it is effective on a small laboratory scale, gaseous ketene is very hazardous to the health of the operator, toxic, and potentially explosive, which makes it highly undesirable for modern industrial usage. In addition, there are significant environmental and economic challenges to methods involving the use of organic solvents, including high cost of solvent recovery, strict VOC emission limits, and the need for strict residual solvent testing in API specification as required by ICH guidelines.

In contrast to catalytic transition-metal systems employing expensive rhodium, palladium, or cobalt complexes [28], [33], our strategy completely eliminates noble metal catalysts, eliminating the risk of heavy metal contamination in the final API product. Continuous-flow microreactor synthesis [12] or microwave-assisted solvent-free techniques [39] have been used to obtain rapid reaction rates, but often require expensive, specialized equipment, limiting the ease of straightforward technology transfer to conventional multi-purpose batch pharmaceutical reactors.

In comparison to recent developments and patent disclosures in the field of industrial green chemistry (e.g. Gourdon and Autret [23]), the optimized process here presented presents several practical advantages:

- **Environmental Safety & Cost Savings:** Both N-acylation and catalytic thermal racemization are performed in a strictly aqueous environment to eliminate the need for organic solvents. Water is also a non-toxic, non-flammable, and cheap reaction matrix, drastically curbing hazardous waste disposal costs.
- **Process Efficiency & High Yield:** The direct utilization of the wet cake of N-acetyl-L-leucine intermediate from Step 1 into Step 2 avoids intermediate drying steps, significantly shortening total cycle time and reducing energy requirements. The overall process yield of **87.28%** at the 1 kg/batch scale surpasses typical multi-step industrial outputs (70%–80%).
- **Product Quality & Regulatory Compliance:** The entire process avoids toxic additives or organic catalysts, resulting in an API purity of 98.1% with heavy metal content below 20 ppm and zero residual solvent concerns.

In general, this comparison shows that the water-based batch technology is safer, environmentally friendly, highly scalable, and an economically better platform for an industrial-scale NAL manufacturing.

IV. CONCLUSION

In summary, an optimized, water-based, and environmentally friendly synthetic process for pharmaceutical-grade N-acetyl-DL-leucine from readily available L-leucine was successfully developed and scaled up to a 1 kg/batch production level [1]. The two-step batch synthesis comprising N-acylation of L-leucine with acetic anhydride followed by catalytic thermal racemization was systematically optimized to maximize yield, process scalability, and product quality [1]. The operational parameters established for industrial scale-up included an acylation temperature maintained below 45°C with a molar ratio of Ac_2O:L-leucine $= 2.1:1$, precipitation at pH $= 3$, and complete racemization at 90°C for 5 hours using a 1:1 molar ratio of Ac_2O to N-acetyl-L-leucine [1]. The scale-up process demonstrated high stability, excellent reproducibility, and cost-effectiveness [1]. At the 1 kg/batch scale, the process achieved an overall yield of 87.28% with an active pharmaceutical ingredient (API) assay purity of 98.1% [1]. The chemical structure of the synthesized compound was unambiguously validated by FTIR, ESI-MS, ^{1}H-NMR, and ^{13}C-NMR spectroscopies, while polarimetry confirmed complete conversion to the racemic form ($[\alpha]_D^{20} = 0°$) [1]. All testing parameters complied fully with in-house quality standards and pharmacopoeial specifications [1]. This green, water-based batch technology provides an industrially feasible route to eliminate reliance on imported raw materials and support domestic API production [1].

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