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Optimized and Scalable Synthesis of Nalbuphine from Noroxymorphone: A Comparative Study of Organic Solvent and Ionic Liquid Media

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Abstract

Nalbuphine is a clinically important semi-synthetic opioid analgesic that offers effective pain relief with a lower incidence of respiratory depression and pruritus than morphine. In the present work, a two-step route to nalbuphine, starting from noroxymorphone, was developed and optimized. The first step consisted of selective N-alkylation of noroxymorphone with cyclobutylmethyl bromide, and the second step involved reduction of the C6 carbonyl group of the resulting nalbuphone. Solvent, base, temperature, reaction time, and molar ratio were varied systematically to identify the optimal conditions. Three n-butyl-substituted ionic liquids—1-butylpyridinium bromide, 1-butyl-3-methylimidazolium bromide, and diethyldibutylammonium bromide—were prepared and tested as alternative reaction media. Although these ionic liquids displayed high thermal stability and could be recycled for up to three runs with > 93% recovery, their high viscosity led to mass-transfer limitations and gave lower isolated yields (up to 74%). Under the optimized conditions, N-alkylation in N-methyl-2-pyrrolidone (NMP) with triethylamine as base at 80°C for 12 h produced nalbuphone in 79% yield. Reduction of nalbuphone with $NaBH_4/I_2$ in tetrahydrofuran (THF) under reflux for 12 h afforded nalbuphine in 80% yield with an α:β epimer ratio of 75:25. The structures of all compounds were confirmed by FT-IR, ^{1}H-NMR, ^{13}C-NMR, and GC-MS. Green chemistry metrics, including E-factor, Process Mass Intensity (PMI), Atom Economy (AE), and Reaction Mass Efficiency (RME) were calculated and compared for both the NMP and ionic liquid routes; the IL route showed a lower E-factor (513 *vs.* 667) and PMI (514 *vs.* 668), while the NMP route gave a slightly higher overall yield (63% *vs.* 59%). The comparison of NMP and ionic liquid media highlights the trade-offs between synthetic efficiency, reaction kinetics, and environmental impact, and provides a scalable basis for greener pharmaceutical synthesis, as demonstrated by a 10 mmol scale experiment (63% overall yield for the NMP route and 59% for the IL route). A complete mass balance was constructed for both steps, with an overall closure of 99.8%, confirming that essentially all input materials are accounted for in the product and waste streams.

1. Introduction

Nalbuphine (commercially known as Nubain) is a semi-synthetic agonist–antagonist opioid of the morphinan class, widely used for moderate to severe pain, particularly in surgical patients and those with cancer [1, 2]. This compound is chemically related to naloxone, and the cyclobutylmethyl substituent on the nitrogen ring is responsible for its potent analgesic activity [3]. Nalbuphine acts primarily as a κ-opioid agonist and μ-opioid antagonist, resulting in analgesia with reduced side effects such as respiratory depression, pruritus, nausea, vomiting, and urinary retention compared with morphine [4, 5]. It is used in many countries, including the United States, the Philippines, Hong Kong, Malaysia, Singapore, South Africa, New Zealand, and several Latin American countries [6].

From a synthetic perspective, nalbuphine is generally synthesized from noroxymorphone, which is obtained from thebaine or oripavine [7]. The main industrial approaches to nalbuphine rely on the coupling of noroxymorphone with cyclobutylmethyl bromide in volatile organic solvents such as DMF, DMSO, or acetonitrile, in the presence of inorganic bases (K_2CO_3, $NaHCO_3$) and iodide promoters (KI, NaI) [8, 9]. Although these protocols deliver moderate to good crude yields (50–75%), they suffer from serious environmental and operational drawbacks [10]. These include long reaction times (often more than 48–96 h), large volumes of toxic high-boiling aprotic solvents, multi-step aqueous work-ups, and no possibility of catalyst or solvent recycling [11]. In addition, they generate large amounts of salt-laden aqueous waste, which conflicts with the principles of modern industrial green chemistry [12].

So far, only a handful of synthetic routes to nalbuphine have been described. Machara et al. [13] synthesized nalbuphine from oripavine in five steps with an overall yield of 45%. The route began with alkylation of oripavine using cyclobutylmethyl bromide, followed by N-demethylation with t-BuONa and t-dodecanethiol in DMSO (73% yield). Oxidation with peracetic acid and subsequent hydrogenation gave nalbuphone (82% yield), and final reduction with H_2/PtO_2 afforded nalbuphine (86% yield). In our previous work, we reported a five-step synthesis of nalbuphine from thebaine, which involved the conversion of thebaine to oxycodone (80% yield), oxycodone to oxymorphone (55% yield), demethylation using ethyl chloroformate to obtain noroxymorphone, N-alkylation with cyclobutylmethyl bromide (82% yield), and final reduction to nalbuphine (75% yield), with an overall yield of approximately 27% [14]. While this route established a viable synthetic pathway, it suffered from a long

sequence, the use of ethyl chloroformate, and moderate overall efficiency. The present work directly builds upon this foundation by developing a significantly shorter two-step route from noroxymorphone, eliminating the need for ethyl chloroformate, and introducing ionic liquids as alternative reaction media for the first time. Zhang et al. [15] used a Ru-catalyzed N-alkylation and $LiAlH_4$ reduction. Mitchell et al. [16] employed Pd/H_2. Most of these methods rely on expensive or toxic catalysts, long sequences, or harsh conditions.

Very recently, we reported a comparative study on the ionic-liquid-assisted synthesis of azaperone, a butyrophenone-class veterinary sedative, in which three n-butyl-substituted ionic liquids were evaluated as alternative reaction media [17]. The present work extends this methodology to the synthesis of nalbuphine, a morphinan-class human analgesic, and demonstrates the generality of the ionic liquid approach for different classes of pharmaceutical compounds. In addition, the mass balance and green metrics are reported for both routes, providing a comprehensive comparison. The present work is therefore aimed at addressing two gaps simultaneously: (i) the systematic use of task-specific ionic liquids as alternative reaction media for this class of butyrophenone derivatives, and (ii) the optimization of a short two-step route from noroxymorphone that avoids precious metal catalysts in the reduction step and provides a quantitative green chemistry assessment. To the best of our knowledge, this is the first report on the use of ionic liquids for the synthesis of nalbuphine. These features not only lower the environmental footprint but also shorten the overall reaction time from 96 h to 12 h per step. In addition, ^{1}H-NMR spectroscopy was employed to determine the α/β epimer ratio formed during the reduction step in different solvents, which allowed selection of THF as the optimal solvent for favoring the desired α-epimer (75:25). Furthermore, purification by recrystallization effectively removed the β-epimer, affording the pure α-epimer as white crystals.

Ionic liquids have emerged over the last two decades as promising alternatives in pharmaceutical synthesis because of their negligible vapor pressure, high thermal stability, and tunable polarity, which allow them to act simultaneously as reaction media and phase-transfer catalysts [18, 19]. For example, Saquib et al. [20] described an ionic-liquid-mediated synthesis of pyrrolobenzodiazepine derivatives, illustrating the potential of these media for pharmaceutically relevant scaffolds. However, their use in the synthesis of butyrophenone-derived veterinary drugs has not been explored so far. Investigating ionic liquids as alternative reaction media for nalbuphine synthesis may therefore provide a more sustainable route without sacrificing synthetic efficiency.

In this paper, we compare two methodological frameworks for the synthesis of nalbuphine: an organic solvent-based system (NMP) and a series of synthesized n-butyl-based ionic liquid matrices. The general synthetic route is shown in Scheme 1. Solvent, base type, catalyst loading, stoichiometry, and temperature were optimized to maximize atom economy, reduce the processing footprint, and evaluate the dual solvent–catalyst behavior of the functionalized ionic liquids.

2. Experimental

2.1. Materials and instrumentation

All reagents, including noroxymorphone, cyclobutylmethyl bromide, triethylamine, N-methyl-2-pyrrolidone (NMP), dimethylformamide (DMF), dimethyl sulfoxide (DMSO), sodium borohydride ($NaBH_4$), iodine (I_2), tetrahydrofuran (THF), pyridine, 1-methylimidazole, diethylamine, 1-bromobutane, 1-butanol, phosphorus tribromide (PBr_3), sodium bicarbonate ($NaHCO_3$), potassium bicarbonate ($KHCO_3$), sodium carbonate (Na_2CO_3), sodium iodide (NaI), potassium iodide (KI), and anhydrous organic solvents, were purchased from Sigma-Aldrich and used as received without further purification. THF was dried over sodium/benzophenone and distilled before use.

Reaction monitoring was conducted via thin-layer chromatography (TLC) on aluminum sheets pre-coated with silica gel 60 F254, visualized under UV light (λ = 254 nm). Melting points were measured on a Büchi B-545 apparatus. Fourier-transform infrared (FT-IR) spectra were recorded on a Perkin-Elmer Spectrum 100 spectrometer using KBr pellets. Gas chromatography–mass spectrometry (GC-MS) analyses were carried out on an Agilent 7890B GC system coupled to a 5977A Mass Selective Detector. Nuclear magnetic resonance (^{1}H-NMR at 400 MHz; ^{13}C-NMR at 100 MHz) spectra were acquired on

a Bruker Avance III spectrometer using $CDCl_3$ or DMSO-d_6 as solvents; chemical shifts (δ) are calibrated against internal tetramethylsilane (TMS). The purity was assessed by GC-MS.

2.2. Synthesis of Task-Specific Ionic Liquids

Three n-butyl-substituted ionic liquids—1-butylpyridinium bromide ([BPy]Br), 1-butyl-3-methylimidazolium bromide ([BMIM]Br), and diethyldibutylammonium bromide ([DEDBA]Br)—were synthesized according to a modified procedure adapted from our previous work [14]. Briefly, 1-bromobutane was first prepared from 1-butanol and PBr_3 in dry acetonitrile (80% yield). Then, [BPy]Br was obtained by alkylation of pyridine with 1-bromobutane in dry acetonitrile at 50°C for 48 h (93% yield). [BMIM]Br was prepared by alkylation of 1-methylimidazole with 1-bromobutane at 70°C for 48 h (93% yield). [DEDBA]Br was synthesized by alkylation of diethylamine with 1-bromobutane in the presence of Na_2CO_3 at 80°C for 48 h (93% yield). The detailed synthetic procedures, workup conditions, and characterization data (^1H and ^{13}C NMR) are provided in the Supporting Information (**Fig. S1–S7**).

2.3. Synthesis of Nalbuphone

In the first step, noroxymorphone was selectively N-alkylated with cyclobutylmethyl bromide to afford nalbuphone. Two alternative reaction media were investigated: NMP and ionic liquids.

2.3.1. Organic Solvent-Mediated Route (NMP)

Noroxymorphone (0.288 g, 1 mmol) was placed in a 100 mL round-bottom flask with triethylamine (0.304 g, 3 mmol) and NMP (5 mL). The mixture was heated at 80°C under reflux for 1 h. Then cyclobutylmethyl bromide (0.244 g, 1.5 mmol) was added, and the reaction was stirred at 80°C for 12 h under nitrogen. After cooling, water (30 mL) and NaCl (3 g) were added, and the mixture was extracted with chloroform (10 mL, then 20 mL). The aqueous phase was acidified with 1 M HCl (5 mL) to pH 1–2 and then basified with 1 M NaOH (5 mL) to pH 8–9. The precipitate was filtered, washed with cold water (10 mL), and dried to give nalbuphone in 79% yield. The estimated total mass of workup reagents is: HCl (0.365 g), NaOH (0.400 g), water (55 g), chloroform (44.7 g). The ^1H NMR, ^{13}C NMR, FT-IR, and GC-MS spectra of nalbuphone are shown in **Fig. S8–S11**.

2.3.2. Ionic Liquid-Assisted Route

In a typical ionic liquid-mediated experiment, noroxymorphone (0.288 g, 1 mmol) and cyclobutylmethyl bromide (0.244 g, 1.5 mmol) were suspended in 5 mL of ionic liquid ([BPy]Br, [BMIM]Br, or [DEDBA]Br). The reaction mixture was stirred vigorously at 80°C under a nitrogen blanket for 12 h. Upon completion, the reaction mixture was treated with cold distilled water (10 mL) and extracted with ethyl acetate (3 × 15 mL). Because of its strong hydrophilicity, the ionic liquid remained in the aqueous phase, whereas nalbuphone was selectively transferred into the organic layer. The combined organic layers were separated, evaporated under reduced pressure, and treated with cold n-hexane to yield nalbuphone (74% for [BPy]Br, 69% for [BMIM]Br, 71% for [DEDBA]Br). The ionic liquid was recovered from the aqueous phase by evaporation of water under vacuum and drying at 60°C for 12 h (50 mbar, then 0.1 mbar), and was reused in subsequent runs without noticeable loss of performance.

2.4. Synthesis of Nalbuphine from Nalbuphone

In the second step, the C6 carbonyl group of nalbuphone was reduced to afford nalbuphine. The reduction was performed using $NaBH_4/I_4$ in THF, and the crude product was purified by recrystallization.

2.4.1. Reduction of Nalbuphone

$NaBH_4$ (0.113 g) and I_2 (0.126 g) were placed in a 50 mL flask in an ice bath, and dry THF (7 mL) was added. After stirring for a few minutes, the mixture turned white. Nalbuphone (0.287 g) was added, and the reaction was refluxed at 70°C for 12 h. After completion (monitored by TLC), the solvent was evaporated, and the residue was partitioned between ethyl acetate (18 g) and water (20 g). The organic phase was evaporated to give nalbuphine as a white solid in 80% yield. The ^1H NMR spectra of the epimer mixtures obtained in THF, DMF, and DMSO are presented in **Fig. S13–S15**.

2.4.2. Purification by Recrystallization

The crude product was further purified by recrystallization: 200 mg of the crude product was dissolved in 10 mL of water at 60°C, and methanol was added dropwise with stirring until complete dissolution. The hot solution was filtered to remove insoluble impurities, and the filtrate was allowed to cool slowly to room temperature to afford pure nalbuphine crystals. The crystals were collected by filtration and dried. The estimated total mass of workup reagents is: ethyl acetate (18 g), water (20 g). The ^{1}H NMR, ^{13}C NMR, and GC-MS spectra of nalbuphine are shown in **Fig. S16–S18**.

2.4.3. Preparation of Nalbuphine hydrochloride salt

To prepare the hydrochloride salt, a measured amount of nalbuphine was placed in a beaker containing sufficient distilled water, and the solution was cooled in an ice bath. Then, hydrochloric acid (HCl) solution was added dropwise with a 1:1 molar ratio relative to nalbuphine. The addition of acid was performed under continuous stirring to prevent sudden temperature increases and to ensure controlled protonation. Upon continued addition of HCl, the initial precipitates gradually dissolved, and the mixture became a clear solution, indicating the formation of the protonated nalbuphine salt. After complete addition of the acid, the reaction mixture was stirred magnetically at low temperature for 2.5 h to complete the salt formation. The progress of the reaction and the complete conversion of free nalbuphine to nalbuphine hydrochloride were monitored by thin-layer chromatography (TLC). The disappearance of the nalbuphine spot and the appearance of the hydrochloride salt spot confirmed the completion of the reaction. After completion and collection of the product, the final amount of nalbuphine hydrochloride was compared with the theoretical value. The reaction yield was approximately 100%, indicating complete conversion of nalbuphine to the hydrochloride salt under the applied conditions.

2.4.4. Gram-scale synthesis (10 mmol scale)

To evaluate the practical scalability of the optimized protocol, the reaction was conducted on a 10-fold scale (10 mmol). A mixture of noroxymorphone (2.88 g, 10 mmol), triethylamine (3.04 g, 30 mmol), and NMP (50 mL) was charged into a 250 mL round-bottom flask. The mixture was heated at 80°C for 1 h, then cyclobutylmethyl bromide (2.44 g, 15 mmol) was added, and the reaction continued for 12 h. After similar workup, nalbuphone was obtained in 79% yield. The reduction was then performed with $NaBH_4$ (1.13 g) and I_2 (1.26 g) in THF (70 mL) to afford nalbuphine in 80% yield with 84% purity (GC-MS). The slightly reduced yield compared to the small-scale reaction (79% vs. 80%) is attributed to less efficient heat and mass transfer in the larger vessel, but the result confirms the practical applicability and robustness of the protocol for preparative-scale synthesis.

3. Results and Discussion

3.1. Optimization of N-Alkylation of Noroxymorphone

The N-alkylation of noroxymorphone with cyclobutylmethyl bromide was optimized as the key step in the synthesis of nalbuphine. This transformation proceeds through an SN_2 mechanism on the amine nitrogen, but the phenolic oxygen can compete and give O-alkylated by-products. Therefore, solvent, base, temperature, molar ratio, and time were systematically varied.

3.1.1. Solvent Screening

A first set of experiments was performed with a 1:1 molar ratio of the two reactants, $NaHCO_3$ as base, and a reaction time of 12 h (Table 1). Polar aprotic solvents such as NMP, DMF, and DMSO gave higher yields because they dissolve both reactants and stabilize the SN2 transition state. NMP gave the best yield (48%), followed by DMF (42%) and DMSO (39%). Protic solvents such as methanol and ethanol strongly suppressed the yield, presumably because hydrogen bonding with the nitrogen reduces its nucleophilicity. Non-polar solvents such as n-hexane and chloroform suffered from poor solubility of the reactants and limited mass transfer. 1,4-Dioxane, although it gave a moderate yield, was considered unsuitable for a green

process because of its toxicity and its ICH Class 2 classification. NMP was therefore selected as the solvent for further optimization.

Table 1
Solvent optimization in the N-alkylation of noroxymorphone

Entry	Solvent	Temperature (°C)	Yield (%)	Purity* (%)
1	Acetone	56	38	82
2	DMF	70	42	–
3	DMSO	70	39	–
4	NMP	80	48	–
5	Chloroform	60	30	–
6	1,4-Dioxane	70	35	–
7	THF	65	28	–
8	Ethanol	70	22	–
9	Methanol	60	18	–
10	Isopropyl alcohol	70	25	–
11	Polyethylene glycol	70	32	–
12	n-Hexane	60	15	–

*Reaction conditions: 1:1 molar ratio of noroxymorphone:cyclobutylmethyl bromide, $NaHCO_3$ as base, time: 12 h, under N_2. Purity determined by GC-MS.

3.1.2. Base Optimization

The effect of the base was next examined under otherwise identical conditions in NMP and DMF (Table 2). Organic bases such as triethylamine and pyridine gave higher yields because of their stronger basicity and their ability to neutralize the liberated HCl. In NMP, Et_3N gave 70%, pyridine 57%, $KHCO_3$ 39%, and $NaHCO_3$ 48%. Inorganic bases, despite providing a basic medium, were less effective because of their lower basicity. Et_3N was selected as the optimal base.

Table 2
Base optimization in the N-alkylation

Entry	Solvent	Base	Temperature (°C)	Yield (%)
1	DMF	Et_3N	80	54
2	DMF	Pyridine	80	51
3	DMF	$KHCO_3$	80	35
4	DMF	$NaHCO_3$	80	42
5	NMP	Et_3N	80	70
6	NMP	Pyridine	80	57
7	NMP	$KHCO_3$	80	39
8	NMP	$NaHCO_3$	80	48

*Reaction conditions: 1.3:1 molar ratio of noroxymorphone:cyclobutylmethyl bromide, time: 12 h, under N_2.

3.1.3. Temperature Optimization

The influence of temperature was then studied in NMP and DMF (Table 3). At room temperature (25°C), essentially no reaction occurred (0% yield), which shows that thermal activation is required to overcome the SN_2 barrier. Increasing the temperature to 50°C gave 50% in NMP and 40% in DMF. At 80°C, the yield in NMP increased to 70%. Therefore, 80°C was selected as the optimal temperature.

Table 3
Temperature optimization in the N-alkylation

Entry	Solvent	Temperature (°C)	Yield (%)
1	NMP	80	70
2	NMP	50	50
3	NMP	25	0
4	DMF	80	54
5	DMF	50	40
6	DMF	25	0

*Reaction conditions: 1.3:1 molar ratio of noroxymorphone:cyclobutylmethyl bromide, Et_3N as base, time: 12 h, under N_2.

3.1.4. Molar Ratio Optimization

Non-stoichiometric ratios were also examined to see whether an excess of one reactant could improve conversion (Table 4). Increasing cyclobutylmethyl bromide from 1.0 to 1.5 equivalents improved the yield from 61% to 79%. A further increase to 1.6 equivalents did not improve the yield (79%). Thus, a 1.5:1 ratio was selected as optimal.

Table 4
Molar ratio optimization in the N-alkylation

Entry	Cyclobutylmethyl bromide (equiv)	Solvent	Yield (%)
1	1.0	NMP	61
2	1.3	NMP	70
3	1.5	NMP	79
4	1.6	NMP	79
5	1.0	DMF	47
6	1.3	DMF	54
7	1.5	DMF	60
8	1.6	DMF	60

*Reaction conditions: Et_3N as base, temperature 80°C, time: 12 h, under N_2.

3.1.5. Reaction Time Optimization

The reaction time was varied in NMP with a 1.5:1 molar ratio and Et_3N (Table 5). The yield was essentially unchanged between 12 and 72 h (79% to 78%). This indicates that the reaction reaches equilibrium after 12 h and that longer times offer no advantage. Therefore, 12 h was chosen as the optimal reaction time.

Table 5
Reaction time optimization in the N-alkylation

Entry	Time (h)	Yield (%)
1	12	79
2	24	79
3	36	78
4	48	78
5	72	79

*Reaction conditions: NMP, Et_3N, 1.5:1 molar ratio, temperature 80°C, under N_2.

3.1.6. Mechanistic Considerations of N-Alkylation

The N-alkylation reaction is a bimolecular nucleophilic substitution (SN_2). The detailed mechanism is as follows: **Step 1: Activation of the nucleophile**. Noroxymorphone possesses two nucleophilic active sites: the secondary amine nitrogen and the phenolic oxygen. Under basic conditions, triethylamine does not deprotonate the nitrogen (secondary amines are not protonated at this pH), but it provides a basic environment for the nitrogen to act as a free nucleophile. NMP, as a polar aprotic solvent, increases the nucleophilicity of nitrogen by removing the protic solvation shell. **Step 2: Nucleophilic attack and transition state formation**. The lone pair of the nitrogen attacks the carbon attached to bromine in cyclobutylmethyl bromide. This attack occurs from the opposite side of the C–Br bond (backside attack), forming a pentacoordinate transition state with trigonal bipyramidal geometry. In this transition state, the N···C bond is forming, and the C···Br bond is breaking. NMP, with high polarity and the ability to stabilize the developing negative charge on bromine, stabilizes the transition state and reduces the activation energy. **Step 3: Leaving group departure and product formation.** The bromide ion leaves as a leaving group, and nalbuphone is formed. The generated HBr is scavenged by triethylamine to prevent protonation of the product nitrogen and formation of a quaternary ammonium salt. Triethylamine also prevents the competing O-alkylation side reaction by controlling the acidity of the medium.

NMP is a polar aprotic solvent with high polarity (ε = 32) and a high donor number. It not only stabilizes the SN_2 transition state but also provides excellent solubility for noroxymorphone (which has polar OH and NH groups) and cyclobutylmethyl bromide (which is relatively nonpolar), providing homogeneous conditions. In contrast, protic solvents such as methanol and ethanol reduce the nucleophilicity of nitrogen by hydrogen bonding, drastically lowering the yield.

3.2. Characterization of Nalbuphone

The ^1H NMR spectrum of nalbuphone (**Fig. S8**) shows aromatic protons at δ 6.65, the C11 proton at δ 4.70, and aliphatic protons between δ 1.56 and 3.11. The ^{13}C NMR spectrum (**Fig. S9**) displays the carbonyl carbon at δ 209.1 and aromatic carbons between δ 117.6 and 143.8. The FT-IR spectrum (**Fig. S10**) contains a broad O–H stretching band at 3370 cm^{-1}, C–H stretching bands at 2823–3021 cm^{-1}, and a strong C = O stretching band at 1728 cm^{-1}, which confirms the presence of the ketone group. The GC-MS spectrum (**Fig. S11**) shows a molecular ion peak at m/z 355.3 $[M + H]^+$, which matches the expected molecular weight of nalbuphone ($C_{21}H_{25}NO_4$, MW 355.4). The ^1H NMR spectrum of the starting material noroxymorphone is provided in **Fig. S12** for comparison.

3.3. Synthesis and application of task-specific Ionic liquids

To explore greener alternatives, three task-specific ionic liquids were synthesized, characterized, and used as alternative reaction media (Scheme 2).

The choice of n-butyl-substituted ILs was guided by their optimal balance of polarity, viscosity, and solvation properties for nucleophilic substitution reactions [17]. Longer alkyl chains (C6–C10) tend to increase the hydrophobicity of the IL, reducing

its ability to dissolve the polar noroxymorphone intermediate, while shorter chains (C1–C2) increase the viscosity and melting point, hindering mass transfer. Furthermore, bromide was selected as the counter-anion based on its known ability to participate in Finkelstein-type halogen exchange, which is expected to accelerate the coupling reaction. In contrast, non-coordinating anions such as BF_4^- and PF_6^-, despite their lower viscosities, are incapable of facilitating this catalytic pathway, as supported by literature reports [18].

The performance of the three ionic liquids as reaction media for nalbuphone synthesis was monitored over 12 h (Table 6).

Table 6
Nalbuphone synthesis performance inside ionic liquids

Entry	Ionic liquid	Temperature (°C)	Yield (%)
1	1-Butylpyridinium bromide	25	0
2	1-Butylpyridinium bromide	80	74
3	1-Butyl-3-methylimidazolium bromide	25	0
4	1-Butyl-3-methylimidazolium bromide	80	69
5	Diethyldibutylammonium bromide	25	0
6	Diethyldibutylammonium bromide	80	71

*Reaction conditions: 1.5:1 molar ratio, time: 12 h, under N_2.

Although the ionic liquids mediated the coupling reaction without any added base or co-solvent, the isolated yields did not exceed 74% under the optimized conditions ([BPy]Br at 80°C). This limitation is mainly caused by the high intrinsic viscosity of the ionic liquid matrices. High viscosity slows down molecular motion and reduces the frequency of effective collisions between the bulky noroxymorphone and cyclobutylmethyl bromide. In addition, strong electrostatic and van der Waals interactions between the ionic liquid clusters and the reactants can over-stabilize them and lower their nucleophilic and electrophilic reactivity. Nevertheless, these systems offer a clear environmental advantage: the ionic liquid can be fully recovered from the aqueous phase by liquid–liquid extraction and reused in successive reactions with almost no loss of performance, which is consistent with the principles of green chemistry.

3.4. Proposed Mechanistic Role of Ionic Liquids

The role of the ionic liquids in the N-alkylation step can be interpreted in terms of three complementary effects, all of which are consistent with the observed trends and the known physical properties of the ILs: (i) Halide-exchange activation. The bromide counter-ion of the IL can participate in a Finkelstein-type exchange with cyclobutylmethyl bromide, generating a more reactive alkyl iodide or alkyl bromide species in-situ. This would accelerate the subsequent SN_2 attack by noroxymorphone. However, because the IL is highly viscous, the mobility of the bromide ion is restricted, so this catalytic effect is partially suppressed compared to a low-viscosity molecular solvent like NMP. (ii) Hydrogen-bonding activation of the amine. For the imidazolium- and pyridinium-based ILs, the acidic C2–H (imidazolium) or α-protons (pyridinium) can form hydrogen bonds with the noroxymorphone nitrogen. This interaction increases the electron density on nitrogen and enhances its nucleophilicity. In [DEDBA]Br, which lacks such acidic protons, this activation pathway is absent, which explains its slightly lower yield (71%) relative to [BPy]Br (74%). (iii) Polarity-driven transition-state stabilization. The high ionic strength and polarity of the IL stabilize the developing charges in the SN_2 transition state, similar to a polar aprotic solvent. However, the same high ionic strength also creates strong Coulombic interactions that can trap the reactants and reduce their mobility, offsetting the accelerating effect.

The net result is that the ILs provide a modest yield (up to 74%) that is lower than that obtained in NMP (79%). Literature-reported viscosity values for these ILs [17, 18] confirm that [DEDBA]Br is the most viscous of the three (156 cP at 25°C and 24 cP at 80°C), which correlates with its lower yield (71%), supporting the mass-transfer limitation hypothesis.

External energy input, such as ultrasound or microwave irradiation, has been reported to overcome such mass-transfer limitations in IL-mediated reactions [19]. Preliminary experiments in our laboratory using ultrasound irradiation showed promising results (82% yield in 24 h), but systematic optimization of these techniques is reserved for future studies.

3.5. Reduction of Nalbuphone to Nalbuphine

The reduction of nalbuphone to nalbuphine was optimized. The C6 carbonyl group can be reduced to either the α- or β-epimer. The aα-epimer is the desired product.

3.5.1. Solvent Screening

The reduction was first examined in different solvents using a 1.2:1 molar ratio of nalbuphone to $NaBH_4$, I_2 as catalyst, room temperature, and 12 h reaction time (Table 7). THF gave the best yield (45%), followed by DMF (40%), NMP (37%), DMSO (30%), and dioxane (28%). Chloroform, pyridine, diethyl ether, and methanol gave no product at all. THF was therefore selected as the optimal solvent.

Table 7
Solvent optimization in the reduction of nalbuphone

Entry	Solvent	Yield (%)
1	DMF	40
2	DMSO	30
3	NMP	37
4	THF	45
5	Chloroform	–
6	Dioxane	28
7	Acetonitrile	–
8	Pyridine	–
9	Diethyl ether	–
10	Methanol	–

*Reaction conditions: 1.2:1 molar ratio of nalbuphone:$NaBH_3$, I_2 as catalyst, temperature 25°C, time: 12 h, under N_2.

3.5.2. Epimer Ratio Screening

Reduction of the carbonyl group in nalbuphone produces alpha- and beta-epimers. The alpha/beta epimer ratio was calculated using ^{1}H-NMR spectroscopy. The signal appearing at 4.2 ppm and 4.0 ppm corresponds to the alpha- and beta-epimer protons. In THF, α:β = 75:25. In DMF, α:β = 67:33. In DMSO, α:β = 49:51. Thus, THF favors the desired alpha-epimer (Table 8). The corresponding ^{1}H NMR spectra are shown in **Fig. S13–S15**.

Table 8
Epimer ratio in different solvents

Entry	Solvent	β:α (%)	α:β (%)
1	THF	25	75
2	DMF	33	67
3	DMSO	51	49

*Reaction conditions: 1.2:1 molar ratio of nalbuphone:$NaBH_4$, I_2 as catalyst, temperature 25°C, time: 12 h, under N_2.

3.5.3. Reducing Agent Screening

Two reducing agents, sodium borohydride and lithium borohydride, were compared (Table 9). The results showed that $NaBH_4$ gave 45% and $LiBH_4$ gave 35%. Therefore, $NaBH_4$ was selected as the optimal reducing agent.

Table 9
Reducing agent optimization in the reduction of nalbuphone

Entry	Solvent	Reducing agent	Yield (%)
1	THF	$NaBH_4$	45
2	THF	$LiBH_4$	35

*Reaction conditions: 1.2:1 molar ratio of nalbuphone:reducing agent, I_2 as catalyst, temperature 25°C, time: 12 h, under N_2.

3.5.4. Temperature Optimization

The effect of temperature was examined with a 1.2:1 molar ratio of nalbuphone to $NaBH_4$, I_2 as catalyst, and a 12 h reaction time under N_2 (Table 10). At 25°C, yield was 45%; at 35°C, 64%; at 45°C, 70%; at reflux, 80%. Therefore, reflux was selected as the optimal temperature.

Table 10
Temperature optimization in the reduction of nalbuphone

Entry	Temperature (°C)	Yield (%)
1	25	45
2	35	64
3	45	70
4	Reflux	80

*Reaction conditions: THF, 1.2:1 molar ratio of nalbuphone:$NaBH_4$, I_2 as catalyst, time: 12 h, under N_2.

3.5.5. Comparison of presence or absence of catalyst

When the reaction was carried out without I_2, the yield dropped to 30%; with I_2, it reached 75%. This difference is due to the in-situ generation of borane (BH_3), which is a stronger reducing agent than $NaBH_4$. The relevant reactions are:

$$NaBH_4 + 2I_2 + THF \rightarrow BH_3{\cdot}THF + NaI + HI$$

3.5.6. Reaction Time Optimization

The reaction time for the reduction was varied (Table 11). In contrast to the initial expectation that a longer time would improve the yield, the yield remained constant at 80% between 12 and 48 h.

Table 11
Reaction time optimization in the reduction of nalbuphone

Entry	Time (h)	Yield (%)
1	12	80
2	24	80
3	36	80
4	48	80

*Reaction conditions: THF, 1.2:1 molar ratio of nalbuphone:$NaBH_4$, I_2 as catalyst, under reflux, under N_2.

3.5.7. Mechanistic Considerations of the Reduction of Nalbuphone

The reduction of the carbonyl group of nalbuphone with $NaBH_4/I_2$ in THF is a multi-step process. The detailed mechanism is as follows:

Step 1: In situ generation of borane (BH_3). $NaBH_4$ reacts with I_2 in THF to produce borane (BH_3). Borane, as a strong Lewis acid, complexes with THF to form BH_3·THF. This complex is a stronger reducing agent than $NaBH_4$ because boron is more electrophilic and transfers hydride more readily to the carbonyl.

Step 2: Activation of the carbonyl. Borane complexes with the carbonyl oxygen of nalbuphone. This complexation increases the electrophilicity of the carbonyl carbon and makes it more susceptible to hydride attack.

Step 3: Hydride transfer. Hydride is transferred from BH_3 to the carbonyl carbon. This transfer occurs through a four-centered transition state in which hydride, boron, and carbonyl are simultaneously involved. The carbonyl is reduced to an alkoxide, and borane is converted to a borinate.

Step 4: Protonation and alcohol formation. The resulting alkoxide is protonated by a proton from the solvent or an available acid to form the corresponding alcohol (nalbuphine).

Epimer formation: Since the C6 carbonyl is planar, hydride can attack from two sides: **Alpha attack**. Hydride attacks from the less hindered side (opposite the bulky groups) to form alpha-nalbuphine (major product). **Beta attack**. Hydride attacks from the more hindered side to form beta-nalbuphine (minor product).

Role of solvent in epimer selection: In THF, the different solubilities of the epimers and solvent–substrate interactions cause hydride attack to be favored from the α side (75:25). In DMSO, higher solubility and stronger solvent–carbonyl interactions change the ratio to 49:51. This observation indicates that stereochemical control is highly dependent on the reaction medium.

Role of I_2

Without I_2, $NaBH_4$ alone is not capable of reducing the carbonyl (30% yield) because $NaBH_4$ has limited solubility in THF and its reactivity is lower. I_2, by generating BH_3 in situ, provides a stronger and more soluble reducing agent, leading to an increase in yield to 75–80%

3.6. Characterization of Nalbuphine

The ^1H NMR spectrum of nalbuphine (**Fig. S16**) shows aromatic protons at δ 6.5 ppm, the C11 proton at δ 4.5 ppm, and the C12 proton at δ 4.0 ppm. The absence of the β-epimer signal at 4.0 ppm confirms that recrystallization effectively removed the β-epimer, affording the pure α-epimer. The ^{13}C NMR spectrum (**Fig. S17**) confirms complete reduction by the absence of the carbonyl peak at δ 209 ppm. The GC-MS spectrum (**Fig. S18**) shows a molecular ion peak at m/z 357.4 $[M + H]^+$,

consistent with the expected molecular weight of nalbuphine ($C_{21}H_{27}NO_4$, MW 357.4). After recrystallization, the β-epimer was effectively removed, and the pure α-epimer was obtained as white crystals.

3.7. Green Chemistry Metrics and Scalability

To provide a quantitative comparison of the environmental performance of the NMP route and the ionic-liquid route, a set of green chemistry metrics was calculated for both pathways (Table 12). These metrics are widely used in pharmaceutical process development to assess sustainability [21]. These metrics include Atom Economy (AE), Reaction Mass Efficiency (RME), E-factor, Process Mass Intensity (PMI), solvent consumption, reaction time, and number of steps. The IL route is represented by [BPy]Br, which gave the highest yield among the three ionic liquids.

Table 12
Comparison of green chemistry metrics for the NMP and ionic liquid routes

Metric	NMP Route	IL Route ([BPy]Br)
Atom Economy (AE, %)	81.5	81.5
Reaction Mass Efficiency (RME, %)	21.5	27.4
E-factor (kg waste/kg product)	667	513
Process Mass Intensity (PMI)	668	514
Solvent consumption (L/g product)	0.55	0.49
Reaction time (h)	12 + 12	12 + 12
Number of steps	2	2

The Atom Economy is identical for both routes because the same chemical transformations are involved. The differences arise from the workup and the reaction medium. The IL route uses no added base in the N-alkylation step, which increases the RME from 21.5% to 27.4%. In addition, the IL route uses less organic solvent in the workup, because the ionic liquid remains in the aqueous phase and the product is extracted with ethyl acetate. This reduces the E-factor from 667 to 513 and the PMI from 668 to 514. The solvent consumption also decreases from 0.55 to 0.49 L per gram of product.

It is important to note that the IL can be recovered and reused for at least three cycles with > 93% recovery. If the IL is recycled, the effective PMI of the IL route is further reduced. For example, if the IL is used three times, the effective PMI of the N-alkylation step becomes approximately 229, which is significantly lower than that of the NMP route. This makes the IL route more attractive from a green chemistry perspective, despite its slightly lower yield (74% vs. 79%).

The NMP route, on the other hand, has a higher yield and shorter reaction time for the N-alkylation step, but it requires a larger amount of organic solvent and a base. The NMP route also generates a larger amount of aqueous waste containing NMP, which is difficult to treat because of its high boiling point and toxicity.

To further support the process assessment, a mass balance was constructed for both steps of the NMP route (**Tables S1–S3**, Supporting Information). The mass balance closure was 99.5% for the N-alkylation step and 100.6% for the reduction step, with an overall closure of 99.8%. These values confirm that essentially all input materials are accounted for in the product, organic waste, and aqueous waste streams. The overall isolated yield of nalbuphine was 63.2% (0.231 g from 0.288 g of noroxymorphone).

The scalability of both routes was demonstrated on a 10 mmol scale. The NMP route gave 2.31 g of nalbuphine in 63% overall yield, while the IL route gave 2.11 g in 59% overall yield. The slightly lower yield of the IL route is offset by its better environmental profile and the possibility of recycling the ionic liquid.

In summary, the NMP route is superior in terms of yield and reaction kinetics, while the IL route is superior in terms of green chemistry metrics and recyclability. The choice between the two routes therefore depends on the specific priorities of the

process: higher productivity (NMP) or lower environmental impact (IL).

3.8. Comparison with Literature

Table 13 compares the optimized protocol with previously reported nalbuphine synthesis methods. The present work offers two routes: the NMP route and the ionic liquid route. Both routes give higher yields (79–80% for NMP, 74% for IL) and shorter reaction times (12 h per step) than most literature methods. In addition, the reduction step avoids precious metal catalysts by using inexpensive $NaBH_4/I_4$. As shown in Table 13, the IL route has better green metrics (E-factor 513 vs. 667, PMI 514 vs. 668) due to the absence of added base and lower organic solvent consumption, although its overall yield is slightly lower (59% vs. 63%).

Table 13
Comparison of the optimized protocol with previously reported nalbuphine synthesis methods

Method	Starting material	Steps	Solvent	Base	Catalyst	Temp. (°C)	Time (h)	Yield (%)	E-factor	Ref.
This work (NMP)	Noroxymorphone	2	NMP	Et_3N	–	80	12	79, 80 (63 overall)	667	–
This work (IL)	Noroxymorphone	2	[BPy]Br	–	–	80	12	74	**513**	–
Machara 2012	Oripavine	4	DMF, DMSO	t-BuONa	PtO_2	80	24–48	88, 73, 82, 86 (45 overall)	~ 8.2	[13]
Taghizadeh 2023	Thebaine	5	DMF, THF	$NaHCO_3$	Pd/C	80	24–48	80, 55, 82, 75	~ 7.5	[14]
Zhang 2020	Noroxymorphone	2	CH_3CN, THF	Et_3N	Ru, $LiAlH_4$	80	12–24	—	~ 9.1	[15]
Mitchell 2012	Noroxymorphone	2	–	–	Pd/H_2	80	24	—	—	[16]

Although the present method avoids noble metals and uses inexpensive $NaBH_4/I_2$ in the reduction step, the NMP route still suffers from high solvent intensity. The IL route offers a greener alternative with lower E-factor and PMI, and the ionic liquid can be recycled. Therefore, the choice between the two routes depends on whether higher productivity (NMP) or lower environmental impact (IL) is preferred. In addition, the mass balance closure of 99.8% (**Tables S1–S3**) provides a level of process accountability that is rarely reported for nalbuphine synthesis, further strengthening the practical relevance of this work. Future work should focus on solvent reduction and recycling for the NMP route and on overcoming the mass-transfer limitations of the IL route.

4. Conclusion

In the present work, several synthetic routes to nalbuphine were examined and the influence of the reaction conditions on the overall yield was systematically studied. Three ionic liquids were synthesized and evaluated as reaction media. By comparing the NMP and ionic liquid routes, this study provides a green and efficient protocol for the semi-synthetic opioid analgesic nalbuphine. The NMP route was the most effective, giving 79% isolated yield within 12 h under mild conditions (80°C) with triethylamine as base. Although the synthesized n-butyl ionic liquids ([BPy]Br, [BMIM]Br, and [DEDBA]Br) showed high thermal stability and could be recycled for up to three runs with > 93% recovery, their high viscosity caused mass-transfer limitations and reduced the isolated yield to 74%. The α/β epimer ratio was determined by ^1H NMR, and THF was selected as the optimal solvent, giving a 75:25 ratio in favor of the desired α-epimer. Recrystallization from a water/methanol mixture effectively removed the β-epimer and afforded pure α-nalbuphine as white crystals. Green chemistry metrics showed that the IL route had a lower E-factor (513 vs. 667) and PMI (514 vs. 668) than the NMP route, mainly because no base was required and less

organic solvent was used in the workup. However, the NMP route still gave a higher overall yield (63% vs. 59%). Nevertheless, their recyclability without significant performance loss makes them economically and environmentally attractive. Although the NMP route currently gives the highest efficiency for nalbuphine synthesis, further structural modification of ionic liquids or the design of new ionic liquids will be needed to overcome the viscosity-related limitations. Preliminary experiments with ultrasound irradiation (40 kHz, 200 W) in [DEDBA]Br at 80°C for 24 h gave nalbuphine in 82% isolated yield, close to the NMP protocol. This suggests that combining ionic liquid media with external energy input (ultrasound or microwave) may overcome the mass-transfer limitations observed here and open new avenues for efficient ionic-liquid-based synthetic protocols. The scalability of the protocol was demonstrated on a 10 mmol scale, giving 2.31 g of nalbuphine in 63% overall isolated yield for the NMP route (59% for the IL route) without loss of efficiency, which confirms its potential for preparative-scale applications. A complete mass balance was constructed for both steps of the NMP route, with a closure of 99.5% for the N-alkylation step, 100.6% for the reduction step, and 99.8% overall. This high degree of mass accountability demonstrates the robustness and practical utility of the developed process. These findings highlight that the choice of reaction medium and operating conditions is critical for efficient synthesis and provide a useful basis for future work on tailoring ionic liquid structures for similar pharmaceutical applications.

Declarations

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Conflicts of Interest / Competing Interests

On behalf of all authors, the corresponding author declares that there are no conflicts of interest.

Data Availability

All information generated or examined during this inquiry is contained in this published article and its supporting information files.

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Schemes

Schemes are available in the Supplementary Files section.

Supplementary Files

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