Full Paper

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Increasing the Purity of Lafutidine Using a "Suicide Substrate"

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Abstract: When preparing lafutidine, we found that the main impurity was dihydro lafutidine. Based on the chemical structure of dihydro lafutidine and the mechanism of its production, we decided to use a "suicide substrate" in the drug preparation to increase the purity of the lafutidine. By calculating the energy barrier of the reduction reaction with a quantum chemical method and evaluating the appropriate physicochemical properties of the terminal olefins, we chose 1-hexene as the "suicide substrate" to effectively control the formation of dihydro lafutidine in the synthesis of lafutidine. The experimental results showed that the content of the impurity, dihydro lafutidine, decreased from 1.5% to less than 0.05%, proving that using a "suicide substrate" is an effective method to reduce the formation of the relevant byproduct in drug production. In addition, this method is operationally simple and is suitable for industrial applications.

Key words: Lafutidine; Dihydro lafutidine; Suicide materials; Terminal olefins.

Introduction Lafutidine (**1**), also named *N*-[4-[4-(piperidinylmetriyl) pyridinyl-2-oxy]-(*Z*)-2-butenyl]-2-(furfurylsulfinyl) acetamide, is a histamine H_2 receptor antagonist that was first produced in Japan by Taiho and UCB Japan for the oral treatment of peptic ulcers in 2000. In 2010, it was approved for the treatment of mild gastroesophageal reflux disease, and in 2012, it was approved to help improve symptoms in gastric mucosal lesion due to gastritis.[1]

Three synthetic routes for preparing lafutidine have been reported in the literature.[2] In Scheme **1**, intermediate **VI** is synthesized from **V** via acetalation.

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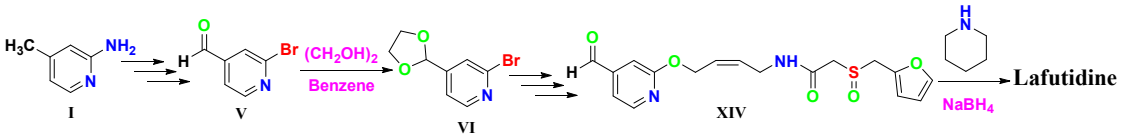
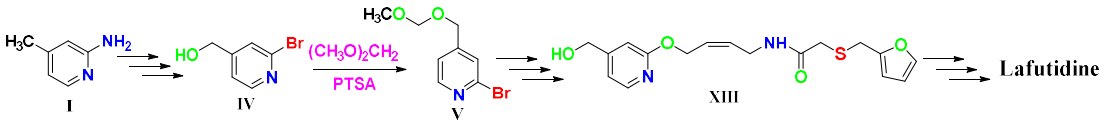
Benzene is utilized as the solvent during the acetalation, which is not environmentally friendly. Additionally, the yields of several steps are relatively low, and the preparation of intermediate **XIV** requires column chromatography purification step, which is not appropriate for industrial manufacturing. In Scheme **2**, benzene is also utilized in the preparation of intermediate **V**. In addition, the crude product of the deprotection in the preparation of intermediate **XIII**, is purified via column chromatography as well. Considering the low yields in several steps, this route is not well suited to large scale manufacture. In addition, these two synthetic routes both start from 4-methylpyridin-2-amine and require 12 steps. Compared to previous routes, the number of synthetic steps in Scheme 3 is reduced to 6 steps with a significant improvement in the yield. Hence, the route is preferred for further industrial exploration.

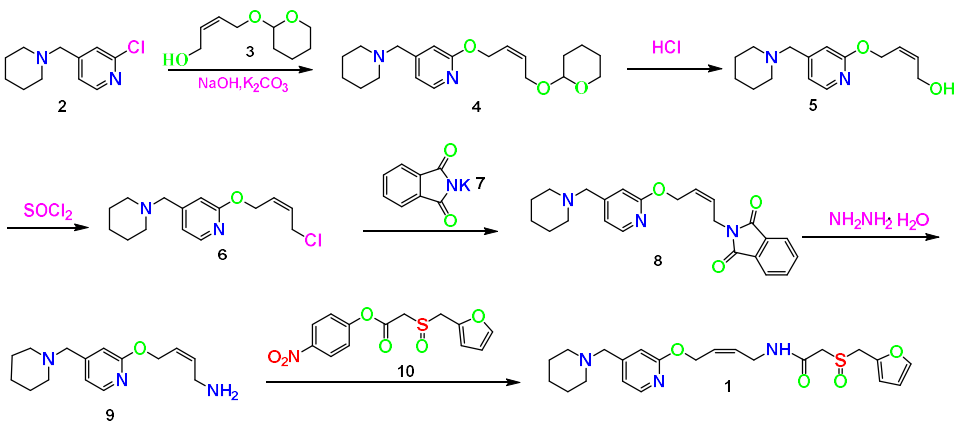


Scheme 1. Reported synthetic route 1 to lafutidine



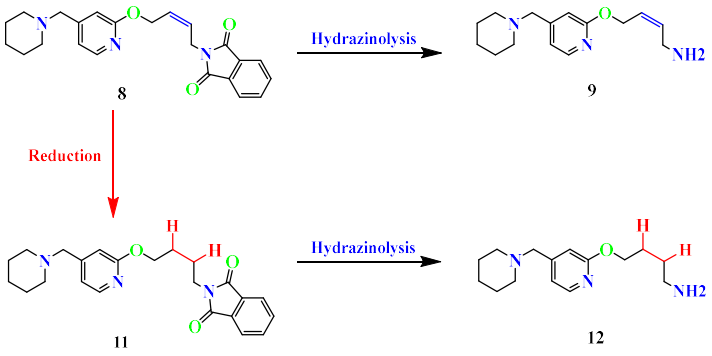
Scheme 2. Reported synthetic route 2 to lafutidine

The synthetic route to lafutidine in Scheme **3** was obtained by modifying method and starting with 2-bromo-4-(piperidin-1-ylmethyl) pyridine (**2**)[3] and inexpensive 4-(tetrahydropyranyloxy)-2-(*Z*)-buten-1-ol (**3**). Starting material **3** was purchased from Beijing Maijin Pharmaceutical Technology Co., Ltd., and it costs approximately 150 dollars per kilogram. Hundreds of kilograms of **1** were produced with good overall yield through this manufacturing route.

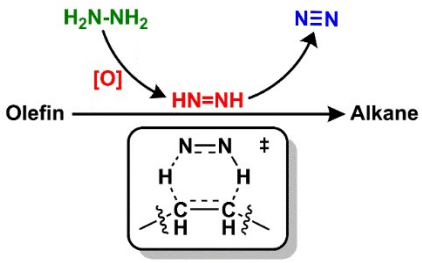


Scheme 3. Reported synthetic route to lafutidine

However, when preparing lafutidine, there was 1.5% to 2% of an impurity by HPLC (Figure **S1**).[4] We assigned the structure of the impurity as dihydro lafutidine, which was separated from the liquid phase and confirmed by mass spectrometry.[5] Based on a study of the preparation process of lafutidine, the dihydro lafutidine impurity was generated during the hydrazinolysis of compound **8**. A plausible pathway was speculated and is shown in Scheme **4**. In the preparation of key intermediate **9**, a small amount of compound **8** was reduced and hydrolyzed to provide compound **12**. Subsequently, dihydro lafutidine was obtained from the condensation of compounds **10** and **12**.



Scheme 4.The process of producing 12



Scheme 5. The mechanism of olefin reduction by hydrazine

Previous reports suggest that hydrazine can reduce olefins in the presence of an oxidizing agent (Scheme **5**).[6] The plausible mechanism of this reduction first involves an oxidation, in which the hydrazine is partially oxidized to the transient diimide. Then, the *cis* isomer of the diimide reduces the unsaturated bond via a nonpolarized six-membered cycloaddition. Subsequently, intermediate **9** would also be reduced by the same mechanism. However, due to the complex reaction mixture, intermediate **8** was easily reduced. In addition, as they are dependent on the reaction mechanism, the reduction and hydrazinolysis could occur simultaneously with minimal interference between each other. Therefore, the reduction of **8** with the diimide was simulated by a quantum chemical method (DFT B3LYP/ 6-31+G(d) level).[7] The transition state structure was obtained with verification of the single imaginary frequency at -981.06 cm^{-1}. The intrinsic reaction coordinate (IRC) also confirmed the plausible mechanism of the diimide reduction. The energy barrier of this reaction was 39.57 kJ • mol^{-1}, which revealed the reduction process could occur under mild conditions. Therefore, during the synthesis of lafutidine, dihydro lafutidine was readily produced (Figure **1**).

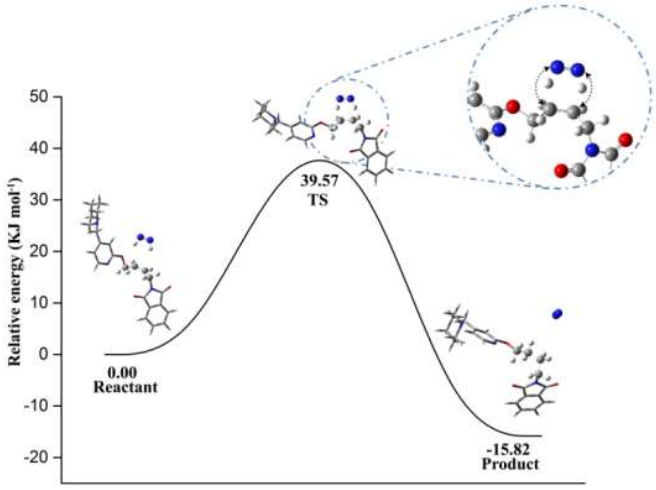


Figure 1. The composite structures of the raw materials and diimine and the appropriate structure of the product.

As seen from all routes, hydrazinolysis is required in the synthesis of lafutidine. Therefore, it is very important to use an effective method to suppress the formation of the hydrogenated product during the hydrazinylation reaction. Previous reports indicate that diimides more easily reduce terminal olefins than internal olefins.[8] A "suicide substrate" is typically used in drug design.[9] We used this concept in the preparation of lafutidine to reduce the formation of the impurity. We chose several terminal olefins as "suicide substrates". The energy barriers of the reductions of the corresponding olefins were determined by theoretical calculations. Table **1** lists the results of the calculations. Compared with **8**, all of the olefins are more reactive in the diimide reduction. Especially for terminal olefins, the energy barriers of these olefins were 10 kJ • mol^{-1} less than that of **8**. This means that terminal olefins can be used as the "suicide substrate" in the diimide reduction.

It was shown that the olefins' energy barriers in the reduction process were approximately 25 kJ • mol^{-1} (Table **1**). All olefins could be used as "suicide substrates". Then, these olefins were tested in the hydrazinolysis process. The corresponding contents of hydrogenated product were determined by HPLC (Table **1**). As a result, the hydrogenation process was effectively suppressed by the olefins except cyclohexene. Furthermore, the physicochemical properties of these olefins were taken into consideration. Compared to other olefins, the boiling points of 1-pentene and 1-hexene are relative lower, which means they can easily be removed during work up. However, 1-pentene is unstable and explosive, which is not preferred for industrialization. In addition, 1-hexene is less expensive than other olefins and is more suitable for industrial production. Based on these facts, 1-hexene was selected as the "suicide substrate" to control the hydrogenation process for further investigation.

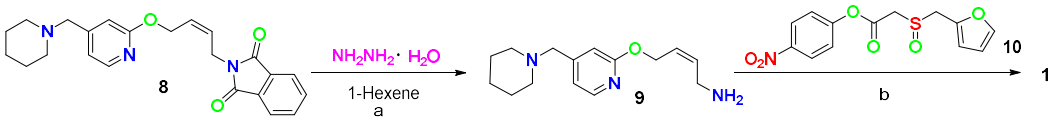
Table 1. The energy barrier of each olefin tested in the reduction process, hydrogenated product (%), price and boiling point.

Olefin	*G* (kJ • mol^{-1})	Hydrogenated product (%)	B.p. (°C)	Price ($/500 mL)
intermediate	39.57416	1.43		
1-pentene	24.74271	0.06	29.9-30.1	213.6
1-hexene	24.50117	0.05	63.4-64.5	28.5

1-heptene	25.36758	0.07	93.6	990.0
1-octene	24.69545	0.05	121	39.1
cyclopentene	26.37315	0.06	83.0	180.0
cyclohexene	37.15608	0.25	44.2	34.8

After choosing 1-hexene as a "suicide substrate", the amount of 1-hexene in the hydrazinolysis reaction was investigated. The addition of two equivalents of hydrazine hydrate was optimal during the hydrazinolysis of intermediate **8**. Only one equivalent of hydrazine hydrate is involved in the hydrazinolysis, and the amount of hydrazine that was oxidized to the transient imide is unknown. Therefore, theoretically, adding at least one equivalent of 1-hexene during the hydrolysis reaction can minimize the formation of the hydrogenated product. Fortunately, excess 1-hexene was easily removed during the experiment. That amount of 1-hexene was investigated in the hydrazinolysis reaction, and the results are shown in **Table 2**. As the amount of 1-hexene increased, the amount of dihydro lafutidine decreased from 1.5% to 0.05% (Figure **S2**). When 1-hexene was added in a 1:1.5 molar ratio to intermediate 8, the content of dihydro lafutidine in the product was minimized (Figure **2**). Therefore, it is more efficient to add 1.5 equivalents of 1-hexene to the hydrazinolysis reaction.

Table 2. Optimization of the Hydrazinolysis Reaction



entry	Hydrazine hydrate (equiv)	1-Hexene (equiv)	Dihydro lafutidine (%, area)[a]
1	2	0	1.50
2	2	1	0.16
3	2	1.2	0.08
4	2	1.5	0.05
5	2	1.8	0.06
6	2	2	0.05

Reaction conditions: a. 8 (23.1 mmol), MeOH (200 ml), stirred at 66 °C for 4 hours; b. 9 (43.6 mmol), THF (260 ml), stirring at room temperature for 18 hours; [a]Percentage of dihydro lafutidine in the reaction mixture, determined by HPLC analysis;

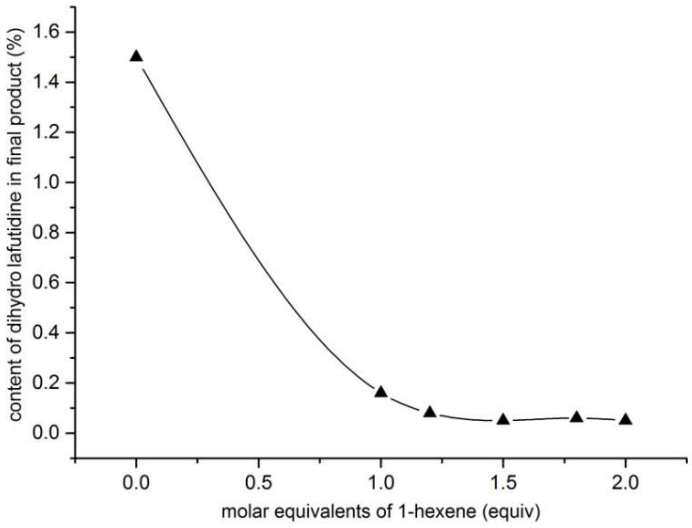


Figure 2. The influence of additional 1-hexene on the generation of dihydro lafutidine

To study the large-scale applicability of this method, six synthetic steps were performed on a kilogram scale. The progress of each reaction was monitored by TLC or HPLC. The content of dihydro lafutidine in the product was determined by HPLC (Figure **S3- S4**). The results of scale-up batches are presented in Table **3**.

Table 3. Results of Scale-up Batches

entry	Batch size Compound 2 (kg)	Output (kg)	Total yield (%)	HPLC purity (%, area)[a]	Dihydro lafutidine (%, area)[b]
1	2.5	1.92	45.7	99.94	0.049
2	2.5	1.89	45.0	99.95	0.042
3	2.5	1.91	45.4	94.94	0.049
4	20	15.8	46.7	99.95	0.047
5	20	16.1	47.5	99.96	0.039

[a,b] % area by HPLC.

Conclusion We proved that the use of a "suicide substrate" is an effective method to reduce the formation of the byproduct in the production of lafutidine. By calculating energy barrier of reduction reaction with the quantum chemical method and the appropriate physicochemical properties of terminal olefins, we chose 1-hexene as a "suicide substrate" to effectively control the formation of dihydro lafutidine in the synthesis of lafutidine. The experimental results showed that the content of impurity dihydro lafutidine decreased from 1.5% to less than 0.05%, and the product's purity was improved. The results of several large-scale experiments confirmed that this method is effective. In addition, this method is operationally simple and suitable for

industrial applications.

Experimental

Quantum Chemistry Calculation Method All optimizations were performed with the Gaussian09 program package.[7] Density functional theory (DFT) was used in the current study using the 6-31+G(d) basis set for all atoms.[7] Frequency calculations were implemented to obtain the thermodynamic data and to verify the transition state. Intrinsic reaction coordinate (IRC) calculations using the Gonzalez–Schlegel second-order method were used to further confirm the TSs.[10] The energy barrier of the reduction process was calculated based on the difference in Gibbs free energy between the reactant and the transition state.

Chemistry The starting materials, reagents, and solvents were all commercially available and used without further purification. The melting points were determined using an X-4 type digital melting point apparatus (thermometer uncorrected). The nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Ascend 400 instrument (Billerica, MA, USA) using tetramethylsilane (TMS) as an internal standard. Electrospray ionization mass spectrometry (ESI-MS) analyses were conducted in an Agilent 1100 Series MSD Trap SL system (Santa Clara, CA, USA). The reactions were monitored by thin-layer chromatography (TLC, HG/T2354-92, GF254). The purity of lafutidine was determined by HPLC using a Shimadzu LC-20A series instrument. HPLC analysis data are reported as relative area percentages and are not adjusted to weight percent.

(*Z*)-4-(Piperidin-1-ylmethyl)-2-((4-((tetrahydro-2*H*-pyran-2-yl)oxy)but-2-en-1-yl) -oxy)pyridine (4)

Toluene (190.0 kg) was added to a 500 L reaction tank. While stirring, **2** (20.0 kg, 78.4 mol), **3** (16.3 kg, 94.4 mol), powdered NaOH (12.5 kg, 312.5 mol), K_2CO_3 (17.5 kg, 125.9 mol) and tetra-*n*-butylammonium hydrogen sulfate (2.5 kg, 7.85 mol) were added to the reaction tank. The reaction was heated to reflux for 15 hours. After cooling to room temperature, the mixture was diluted with 80 kg of toluene. The organic phase was washed with water (120.0 kg x 3) and dried over anhydrous $MgSO_4$ (14.0 kg). The solvent was evaporated *in vacuo* (70-75 °C, -0.093 Mp) to give

a yellow oil (**4**, 23.9 kg, 88.2%).[2]

(*Z*)-4-((4-(Piperidin-1-ylmethyl)pyridin-2-yl)oxy)but-2-en-1-ol (5)

AcOEt (180 kg) was added to a 500 L reaction tank, and **4** (23.0 kg, 66.4 mol) was added while stirring. Hydrochloric acid (1 N, 115 kg) was added to the reaction tank through a 150 L overhead tank, and the reaction mixture was then stirred at 25 °C for 2 hours. The reaction was stopped, and the aqueous phase was separated and washed with AcOEt (90.0 kg x 2). The aqueous phase was adjusted to pH 9 with solid potassium carbonate and extracted with CH_2Cl_2 (120.0 kg x 3). The organic phase was washed with saturated aqueous sodium chloride solution and dried over anhydrous $MgSO_4$ (10.0 kg). The solvent was evaporated *in vacuo* (45–55 °C, -0.080 Mp) to give a yellow oil (**5**, 15.7 kg, 90.0%).[2]

(*Z*)-2-(4-((4-(Piperidin-1-ylmethyl)pyridin-2-yl)oxy)but-2-en-1-yl)isoindoline-1,3-dione (8)

CH_2Cl_2 (200.0 kg) was added to a 500 L reaction tank. **5** (15.0 kg, 57.2 mol) and potassium carbonate (12.0 kg, 85.8 mol) were added with stirring, and the mixture was cooled to 0 °C with cold brine. Thionyl chloride (10.2 kg, 85.8 mol) was diluted with 105.6 kg CH_2Cl_2, and the solution was added dropwise to the reaction through an overhead tank (to ensure that the temperature of the reaction solution was less than 5 °C). The temperature was increased to 25 °C, and the reaction was stirred for 2 hours. Aqueous sodium bicarbonate (170.0 kg, 5% solution) was added, the mixture was stirred, and the layers were separated. The organic layer was extracted with 1.5 N hydrochloric acid (80.0 kg x 3), and the aqueous phase was washed with CH_2Cl_2 (80.0 kg x 2). The aqueous phase was adjusted to pH 9 and extracted with CH_2Cl_2 (100.0 kg x 3). The organic phase was washed with saturated aqueous sodium chloride solution and dried with anhydrous $MgSO_4$ (12.0 kg). The solvent was evaporated *in vacuo* (45–55 °C, -0.080 Mp) to give a yellow oil (**6**). Intermediate **6** was dissolved in 190.0 kg of acetonitrile in a 500 L reaction tank. Potassium phthalimide (10.8 kg, 58.4 mol) and tetra-*n*-butylammonium hydrogen sulfate (1.9 kg, 5.7 mol) were added with stirring, and the mixture was refluxed for 18 hours. The reaction mixture was cooled to room temperature, and the insoluble material was removed by filtration under

pressure. The filtrate was concentrated *in vacuo* (45–50 °C, -0.090 Mp), and the residue was dissolved in AcOEt (140.0 kg). The organic phase was washed with 1 N NaOH (90.0 kg) and then with water (90.0 kg) and dried over anhydrous $MgSO_4$ (10.0 kg). The solvent was evaporated *in vacuo* (45–50°C, -0.090 Mp) to give a crude solid. The crude product was recrystallized from EtOH and dried under vacuum (50 °C, -0.095 Mp) for 3 hours to give **8** (17.4 kg, 78.0%). [2]

(*Z*)-4-((4-(Piperidin-1-ylmethyl)pyridin-2-yl)oxy)but-2-en-1-amine (9)

MeOH (120.0 kg) was added to a 250 L reaction tank, and **8** (17.0 kg, 43.4 mol) was added with stirring. 1-Hexene (5.5 kg, 65.1 mol) was added dropwise to the reaction tank, and 80% hydrazine hydrate (5.5 kg, 86.8 mol) was added to the reaction mixture. The mixture was heated under reflux for 4 hours. The reaction was cooled to room temperature and filtered to remove the insoluble material. The filtrate was concentrated to one-fifth of its original volume, and after standing, the residue crystallized and was dried *in vacuo* (45°C, -0.095 Mp) for 4 hours to give **9** (10.5 kg, 92.5%).[2]

***N*-[4-[4-(Piperidinylmetriyl)pyridinyl-2-oxy]-(*Z*)-2-but-enyl]-2-(furfurylsulf-inyl) acetamide (1)**

THF (106.0 kg) and **10** (12.4 kg, 40.1 mol) were added to a 250 L reaction tank with stirring, and the mixture was cooled to 5 °C. A solution of **9** (10.5 kg, 40.1 mol) in THF (55.0 kg) was slowly added dropwise to the reaction tank through an overhead tank, and the mixture was kept at this temperature for 1 hour. It was then stirred at room temperature for 18 hours and concentrated *in vacuo* (40–45 °C, -0.090 Mp). The residue was taken up in AcOEt (100.0 kg). The solution was washed with 1 N NaOH (50.0 kg) and then water (50.0 kg), dried over anhydrous $MgSO_4$ (8.0 kg), concentrated *in vacuo* (45–50 °C, -0.090 Mp), recrystallized (acetone 19.0 kg) and then dried under vacuum (45 °C, -0.095 Mp) for 2 hours to give **1** as a white solid (15.8 kg, 91.3%)[2,3]: ^{1}H NMR(600 MHz), ($CDCl_3$) δ: 1.43 (m, 2H), 1.56 - 1.60 (m, 4H), 2.36 (m, 4H), 3.34 (d, 1H, J = 14.4 Hz), 3.40 (s, 2H), 3.59 (d, 1H, J = 14.4 Hz), 4.10 (t, 2H, J = 6.6 Hz), 4.17 (d, 1H, J = 13.8 Hz), 4.31 (d, 1H, J = 13.8 Hz), 4.93 (d, 2H, J = 6.6 Hz), 5.67 - 5.69 (m, 1H), 5.83-5.87 (m, 1H), 6.39 (dd, 1H, J = 1.8, 3.0 Hz),

6.47 (d, 1H, J = 3.0 Hz), 6.72 (s, 1H), 6.87 (d, 1H, J = 5.4 Hz), 7.19 (s, 1H), 7.43 (d, 1H, J = 1.8 Hz), 8.03 (d, 1H, J = 5.4 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 24.2, 26.0, 26.0, 37.2, 50.2, 53.4, 54.6, 54.6, 61.4, 62.4, 110.8, 111.3, 112.2, 117.7, 128.4, 128.9, 143.3, 143.9, 146.3, 151.5, 163.6, 163.6. IR (KBr) 3325, 2935, 1638, 1613, 1041 (cm^{-1}). ESI-MS m/z 431.1.

Associated Information

Supporting Information

HPLC spectra of lafutidine ("suicide substrates" were not added during the synthesis process; 1-Hexene was added as a suicide substance during the synthesis process; Large-scale experiments using a 20 L reactor; Large-scale experiment with a 250 L reaction tank); ^{1}H NMR and ^{13}C NMR spectra of Lafutidine

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Notes

The authors declare no competing financial interest.

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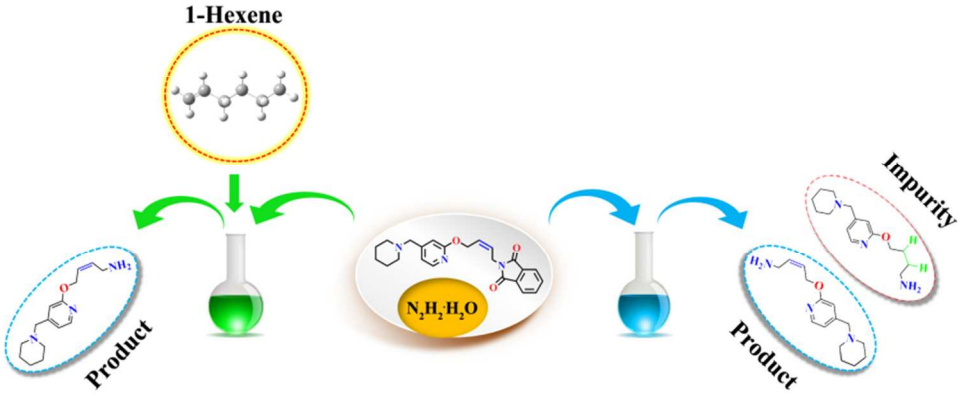

Table of Contents graphic

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