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Process Research and Impurity Control Strategy of Esketamine

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Abstract

An improved synthesis of (*S*)-ketamine (Esketamine) has been developed, which was cost-effective and the undesired isomer could be recovered by racemization. Critical process parameters of each step were identified as well as the process-related impurities. The formation mechanisms and control strategies of most impurities were first discussed. Moreover, the (*S*)-ketamine tartrate is a dihydrate, which was disclosed for the first time. The practicable racemization catalyzed by aluminum chloride was carried out in quantitative yield with 99% purity. The ICH-grade quality (*S*)-ketamine hydrochloride was obtained in 51.1% overall yield (14.0% without racemization) by chiral resolution with three times recycling of the mother liquors. The robust process of Esketamine could be industrially scalable.

Keywords

Esketamine; Major Depressive Disorder; Process; Racemization; Impurity

Introduction

Major depressive disorder has become a common and major public health challenge, and approximately 16% of the world population suffer from depression at some point in their lives[1, 2]. However, the current antidepressants, usually several weeks to months, are necessary to effectively alleviate the clinical symptoms[2]. This significant time lag and unsatisfactory therapeutic efficacy limit the application prospect of current antidepressants. As a result, it is urgent to develop antidepressants with better pharmacodynamics and pharmacokinetics[3, 4].

(2*S*)-(2-chlorophenyl)-2-(methylamino)-cyclohexanone ((*S*)-**1**, (*S*)-ketamine, Esketamine), typically assumed to N-methyl-D-aspartate (NMDA) receptor antagonist, has been approved as a nasal spray formulation for the treatment of major depressive disorder on March 5th, 2019 by FDA. (*S*)-ketamine has higher potency or affinity for the NMDA reception and thus potentially allowing for lower dosages than its enantiomer *(R)*-ketamine.[5]

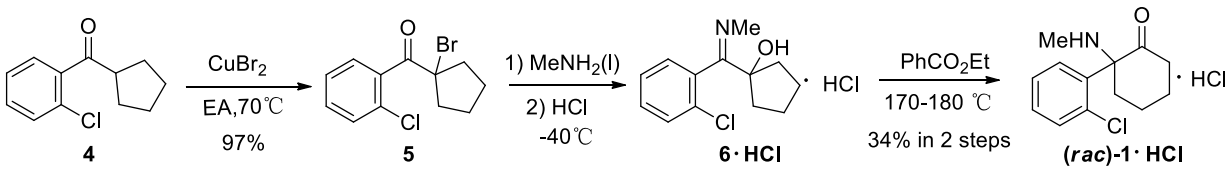
(*S*)-Ketamine is a 3-4 fold more potent inhibitor of the NMDA receptor, which promoted the development of its asymmetric synthesis strategies. For instance, Kiyooka and colleagues [6] reported a procedure for the asymmetric synthesis of (*S*)-Ketamine with an overall yield of 21% (99% e.e.) in ten steps; however, the synthetic route has low atom economy and high energy consumption. Another catalytic asymmetric route with similar idea was reported recently by Chen and colleagues [7]. The procedure, based

on catalytic enantioselective transfer hydrogenation of a cyclic enone and [3, 3]-sigmatropic rearrangement of an allylic cyanate to isocyanate, afforded Esketamine (99% e.e) in 50% overall yield. A concise route designed by Toste [8], starting from *o*-chlorophenyl cyclohexanone, using direct asymmetric electrophilic amination with di-tert-butyl azodicarboxylates to install the desired quaternary stereocenter, was conducted in three steps with 30% yield (99% e.e.). The key step was carried out at 40 °C for 50-60 h and relied on the complex chiral organophosphorus ligands which have not yet been industrialized. More recently, Gohari[9] utilized Ellman's (*S*)-tert-butanesulfinamide as a chiral auxiliary to form the stereocenter following Grignard reagent as nucleophile at -78 °C, and (*S*)-**1** was synthesized under ozonolysis condition and gave the unsatisfactory 75% ee.

Although several asymmetric syntheses of Esketamine have been reported, an efficient and scalable synthesis to enantiopure Esketamine was desired. Classical resolution[10] of the *rac*-**1** could be a better choice for the industrialization of (*S*)-**1** if the unwanted (*R*)-**1** isomer lost in the mother liquor could be racemized. Recently, another economical and environmental process for the preparation of racemic ketamine under sustainable continuous flow conditions was reported by Monbaliu. However, it should be emphasized that the final step was carried out on Montmorillonite K10 with a high pressure (35 bar) and high temperature (180 °C), and the conversion of was the unsatisfactory 57-75%, leading to a low yield 62%[11b]. Considering the productivity and cost of three procedures [11-12], the general route reported by Stevens and colleagues[12]

was more suitable for further investigation of scale-up (**Scheme 1**).The process involved a bromination-imination-thermal rearrangement sequence and was adopted for the preparation of ketamine analogs by the Janssen Pharmaceutical Company in the laboratory [13]. However, the bromination step was typically poor atom economy with the using of N-bromobutanimide[14], bromine[15] or copper bromide[13]. Subsequently, the corresponding intermediate **5** was next subjected to further imination which usually carried out with excessive liquid methylamine at low temperature -40 °C. During the thermal rearrangement step, α-hydroxyimine **6** hydrochloride was heated to 170-180 ° C in decalin. Herein, a modification of the general route for ketamine, followed by a chiral resolution, was developed with the aim of industrially scalable and raising the product quality.

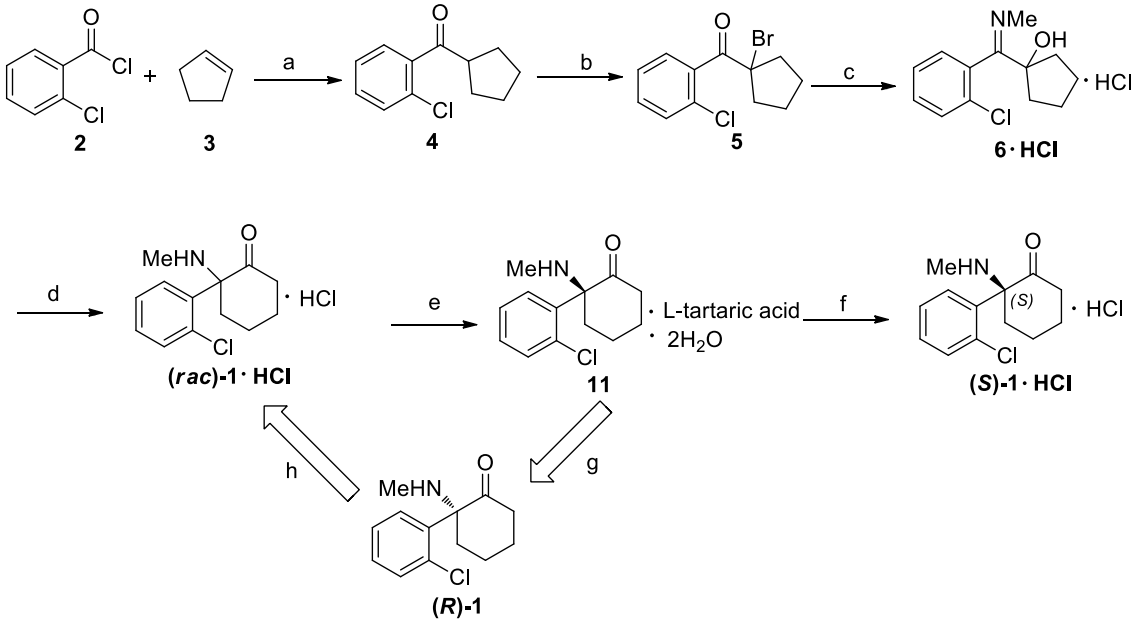
Scheme 1. The General Route of **(*rac*)-1**



Results and Discussion

We herein report an improved synthetic route for the preparation of (*S*)-**1** with the racemization of unwanted (*R*)-**1**, as shown in Scheme **2**.

Scheme 2. Improved Synthetic Route to Esketamine **(*S*)-1**[a]



[a] Reagents and conditions: (a) (1) $AlCl_3$, CH_2Cl_2, −10°C, (2) $AlCl_3$, cyclopentane, 40 °C, 3 h, vacuum distillation,70.3%; (b) 48% HBr, 30% H_2O_2, 70-80 °C, 3 h, 96.8%; (c) (1) 15-20% CH_3NH_2 aqueous solution, 15-20 °C, 48 h, 90%; (2) 2 N EA-HCl; (d) PhCOOEt, $AlCl_3$, 125 °C, 5 h, 93.6%; (e) L-(+)-tartaric acid, acetone/H_2O, 41%; (f) (1) NaOH,; 2 N EA-HCl; (2) crystallized with acetone /H_2O, 80%; (g) 1N NaOH (aq); (h) (1) 2 N EA-HCl in EA; (2) 10 mol % $AlCl_3$; PhCOOEt, 150 °C, 24 h, 99%.

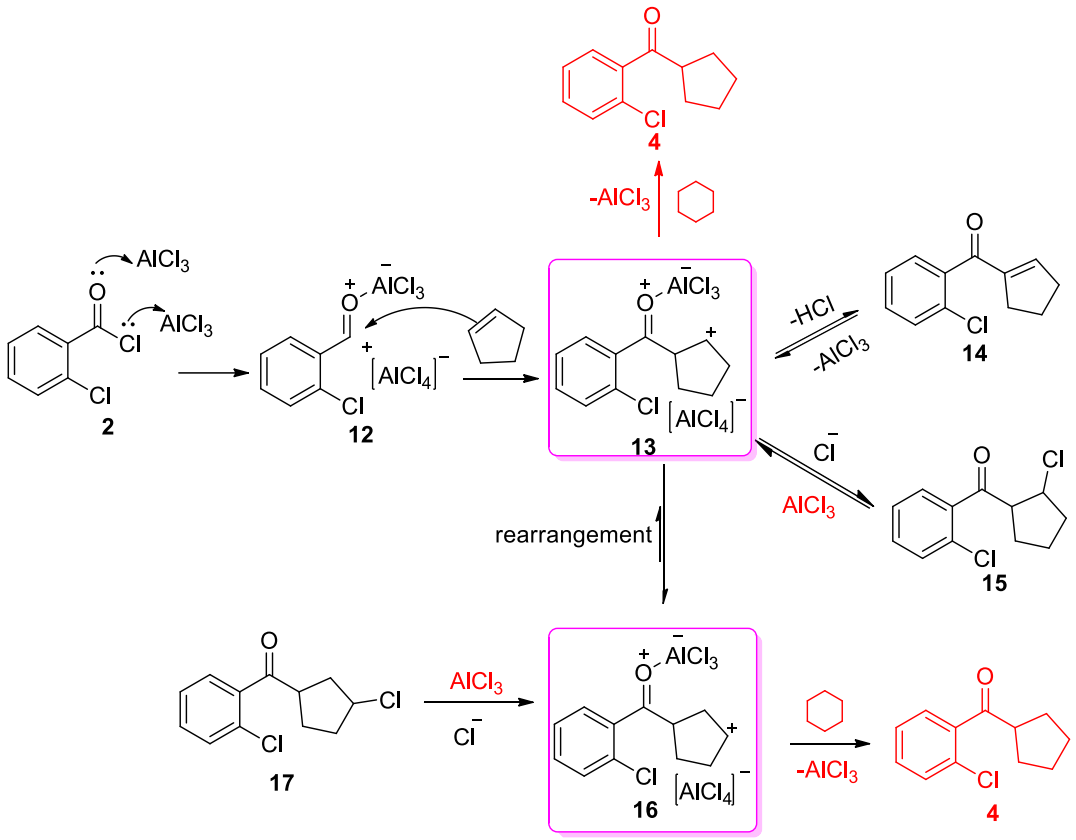
Preparation of (2-chlorophenyl) cyclopentyl ketone (4)

It was reported that **4** was synthesized via Grignard reaction using *o*-chlorobenzenitrile and cyclopentyl magnesium bromide as raw materials. However, the anhydrous and anaerobic conditions are always required for Grignard reaction, which necessitate rigorous equipment and operation controls. Moreover, the relatively high

price of bromocyclopentane (14.3 K U.S. dollars per ton in China) and large dosage (>1.5 equiv) in the reaction increase the cost. Furthermore, the yield of Grignard reaction was not high (68%) [14]. All above these prompted us to explore other processes to synthesize **4**. The Nenitzescu Reductive Acylation is one of the important methods to prepare ketones with mild reaction conditions, and the raw materials used are cheaper than bromocyclopentane. Therefore, the cheaper *o*-chlorobenzoyl chloride and cyclopentene were used to replace Grignard reagent as raw materials to prepare **4** via Nenitzescu Reductive Acylation reaction [16-17].

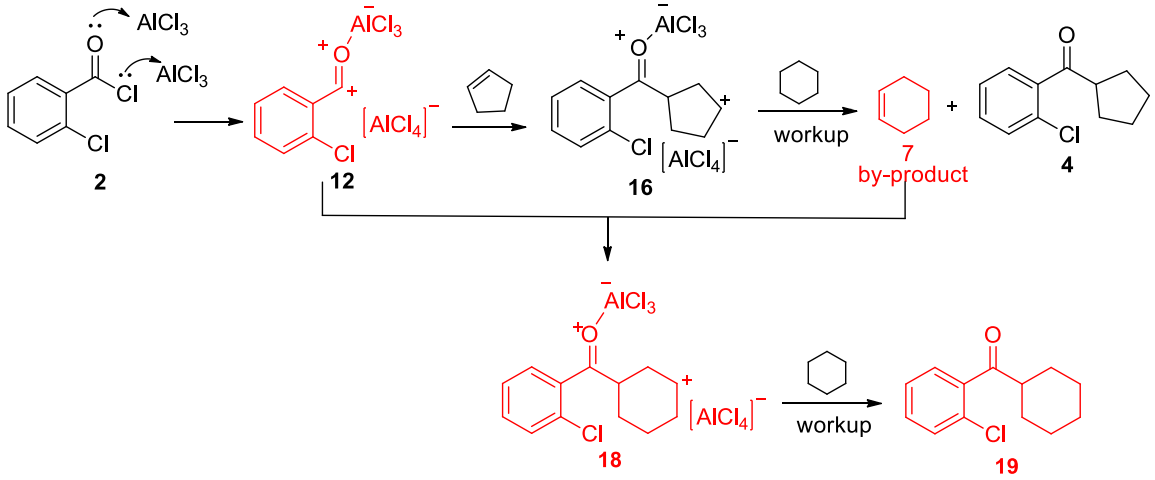
In the general procedure for the reductive acylation reaction, two moles of aluminum chloride ($AlCl_3$) were added to a mixture of the olefin and acyl chloride in cyclohexane solvent at about -l0 °C, and upon warming slowly to 70 °C, HCl was evolved and the saturated ketone was obtained [16-17]. The probable mechanism for the preparation of **4** was shown in **Scheme 3**. The reaction process was divided into two stages, and the intermediates **14**, **15**, **17** were obtained via Friedel Crafts acylation in the first stage. When acyl chloride **2** was completely converted to the intermediate states, another batch of $AlCl_3$ was added, and **14**, **15**, **17** returned to carbocation **13** or **16** through Friedel crafts alkylation, and then the product **4** was obtained after the reduction of saturated alkane. The intermediates **14, 15, 17** were separated from the reaction mixture and structures characterized by HRMS and NMR spectra, which are shown in the Supporting Information.

Scheme 3 the Probable Mechanism for the Preparation of **4**



Under the above conditions, a larger impurity **19** was detected at approximately 21.2% on LC-MS, respectively. According to the corresponding molecular weight 222.1, the impurity was generated as a result of the competitive reaction between cyclopentene and the byproduct cyclohexene produced from the dehydrogenation of cyclohexane in the reaction mixture. The formation mechanism of **19** was proposed as show in **Scheme 4**. Therefore, the cyclopentane was a good substitute for cyclohexane to avoid the generation of impurity **19**. Moreover, dichloromethane was used to replace cyclopentane as solvent to improve the reaction and reduce the amount of $AlCl_3$ due to the better solubility for $AlCl_3$.

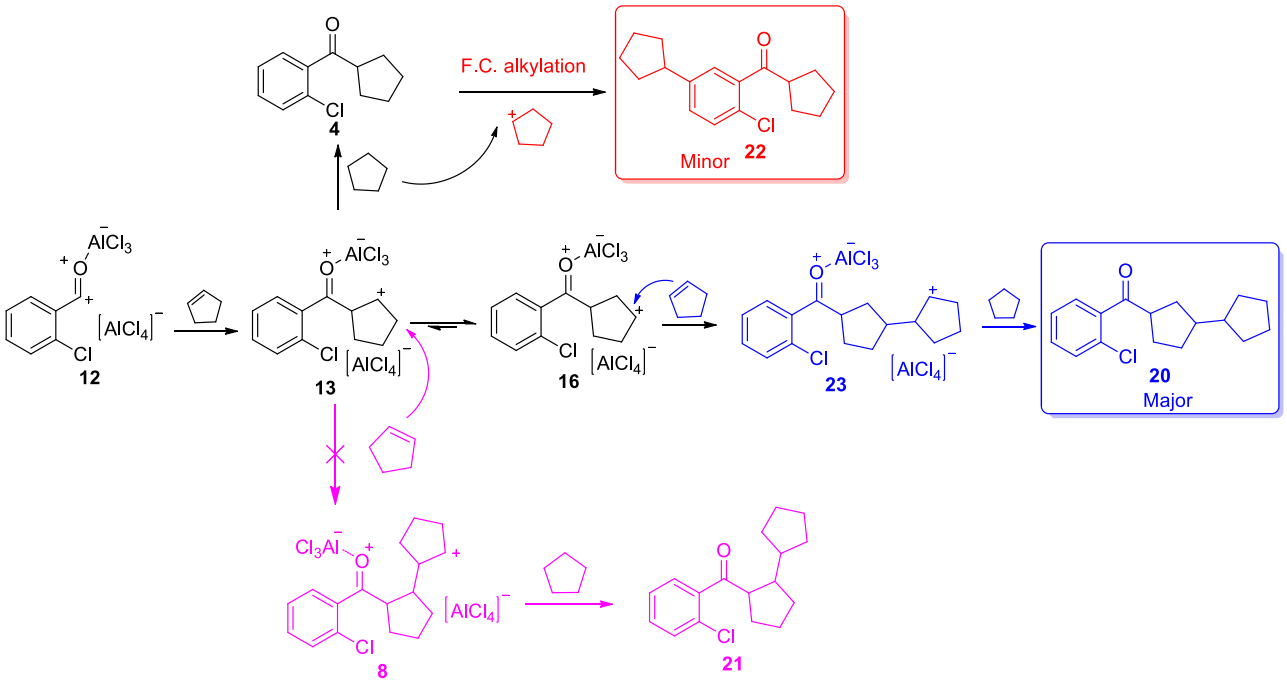
Scheme 4. The Proposed Formation Mechanism of Impurity **19**



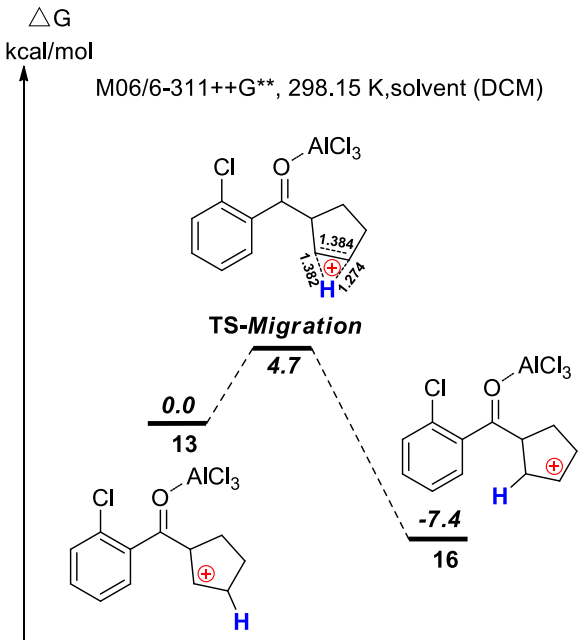
Another two impurities were also detected, of which molecular weights detected by LC-MS were both 276.1, just one more cyclopentane than that of **4**. The two impurities were presumed to be **20** and **21**, and the formation mechanisms were proposed as show in **Scheme 5**. The two compounds with indefinite structures were obtained by the preparative chromatography and then characterized by 1D and 2D NMR spectra. However, the structures were confirmed as compounds **20** and **22** rather than **21**. According to the results, we speculate that the carbocation **16** was more stable due to the γ position being less affected by the electronegativity of carbonyl group. The stability of reactive intermediates **13** and **16** was supported by Density Functional Theory (DFT) calculations and the Gibbs free energy was 0.0 kcal/mol and - 7.4 kcal/mol, respectively **(Scheme 6)**. **16** was easily obtained from the rearrangement of **13** through the transition state of TS migration. The free energy profiles of both carbocation were calculated by the M06 method[18] in dichloromethane (DCM). Even if

two electron withdrawing substituents are attached to the benzene ring, the impurity **22** was still generated via Friedel-Crafts alkylation.

Scheme 5. The Proposed Formation Mechanism of Impurities **20** and **22**

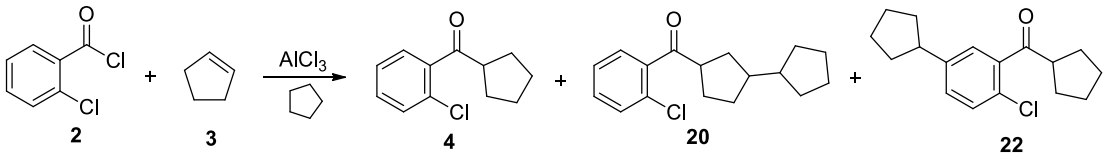


Scheme 6. Free-Energy for 13 and 16



In view of the above analysis, the carbocation **16**, competing with acetyl cation **12**, would react with cyclopentene in the reaction mixture, and **20** was obtained after further hydrogenation. Undoubtedly, the electrophilicity of **12** is stronger than **16**. In view of the reaction mechanism, the equivalent of cyclopentene was reduced, which will cause part **12** not to be involved in the acylation, so that the newly generated cyclopentene would react with unreacted **12** first rather than **16**. Moreover, the reaction time was strictly controlled to 3 h, because of the tendency of impurities **20** and **22** to increase gradually with the reaction time prolonging (**Table 1,** entry 4). The results were summarized in Table **1**.

Table 1. Nenitzescu Reductive Acylation under Various Conditions [a]



Entry	equivalence ratio	HPLC (%)[b]		
	2 : 3	**4**	**20**	**22**
1	1:1.4	78.3	15.3	6.4
2	1:1.1	92.1	5.8	2.1
3[c]	1:0.9	63.8	11.2	2.3
4[d]	1:1.1	81.9	12.6	5.5

[a] Reaction conditions: $AlCl_3$ (1.1+1.2 equiv) were added in two batches, solvent: CH_2Cl_2, reaction time: 3 h, reductant: cyclopentane. [b] Only peak areas (%) of **20**, **22** and **4** were integrated; [c] Peak areas (%) of **2, 4, 20** and **22**were integrated, 22.7% of **2** remaining, reaction time was prolonged to 6 h; [d] the reaction time was prolong to 6 h.

The workup procedure involved adding the reaction mixture slowly to cold water followed by 10-15% sodium hydroxide aqueous solution to remove $AlCl_3$, and the brown oily liquid was obtained in the purity 87.2% after the dichloromethane was concentrated under reduced pressure. In order to improve the purity of the product and remove the residual $AlCl_3$, **4** was purified to a pale yellow liquid with high purity of 98.7% on HPLC by vacuum rectification (2 mmHg, 116-120 °C fraction). Intermediates **15** and **17** were removed during the vacuum distillation process and the impurities **14**, **20** and **22** were all reduced to be less than 0.8% by HPLC analysis.

Preparation of (1-bromocyclopentyl) (2-chlorophenyl) ketone (5).

The bromination step was typically poor atom economy with the using of N-bromobutanimide (NBS) [14], bromine (Br_2) [15] or copper bromide ($CuBr_2$) [13]. The raw material costs, conversion rate, waste streams and risk factors for various industrial bromination reagents, are presented in Table **2**. After comprehensive comparison, we finally chose hydrogen bromide (HBr) in combination with hydrogen peroxide (H_2O_2) as the bromination reagent with high atomic economy, less environmental pollution and low cost for bromination reaction. The bromine anion was oxidized by H_2O_2 and

completely transferred to **5**. The by-product was only environment-friendly H_2O, which saved the cost of waste disposal comparing to the other bromination reagents.

Table 2. The Comparison of Various Bromination Reagents for the preparation of **5** [a]

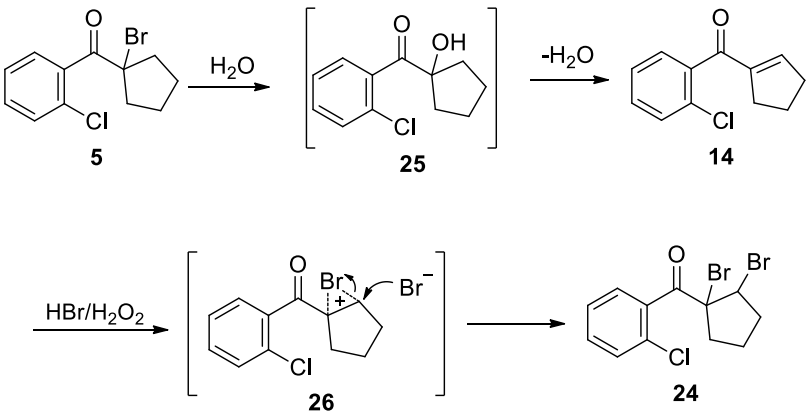
Entry	Br source	Br utilization rate	Stoichiometric reagents required	Cost [b]	Waste stream	Hazard factor [c]	Conversion rate[d]
1	$Br_{2(l)}$	50%	Br_2	middle	HBr	high	15%
2	$CuBr_{2(s)}$	50%	$CuBr_2$	high	CuBr	low	99%
3	$NBS_{(s)}$	100%	NBS+*p*-TsOH	high	succinimide	low	88%
4	$HBr_{(l)}$	100%	$2HBr+H_2O_2$	low	$4H_2O$	middle	95%
5	$KBr_{(s)}$	100%	$2KBr+H_2O_2+H_2SO_4$	low	$4H_2O+K_2SO_4$	low	89%

[a] Based on the reaction "**4**" + XBr ⟶ "**5**"; [b] Prices from the latest quotation in China (¥ ton^{-1}): bromine (l) 75,000; $CuBr_2$ 125,000; NBS 58000; KBr 36,500; HBr (48 wt % aq) 20,000; hydrogen peroxide (30 wt % aq) 7,500; [c] Reaction /storage risks; [d] HPLC purity of the reaction mixture.

In view of the similarity between the oxidative bromination on activated aromatics reported in the literature[19] and the bromination of **4**, both 1.0 equivalent HBr and H_2O_2 was explored. However, the reaction did not reach completion with the H_2O_2 dripping slowly, approximately 14.2% ketone remained by HPLC, as shown in Table **3** (entry

1). The bromine, which formed inevitably during the reaction process, guided us to increase the amount of hydrogen bromide. Subsequently, when the equivalent of HBr and H_2O_2 were increased to 1.5, the conversion rate was still the unsatisfactory 95% (Table **3** entry 2). The addition of excessive HBr and prolonging the reaction time will lead to an increase of impurity **24**, whose proposed formation mechanism was shown in the **Scheme 7**. Compounds **25** and **14** were detected in the reaction solution by HPLC with the content of 0.2% and 1.0%. HRMS and NMR spectra of **24** are displayed in the Supporting Information. The mixing speed and temperature were two major factors responsible for the incomplete reaction, the faster the stirring speed, the greater the reaction rate. The best result was obtained under the conditions that maintain the reaction temperature at 70-80 °C by adjusting the dropping speed of 1.5 equiv hydrogen bromide at the stirring speed of 400 rpm (Table **3**, entry 3).

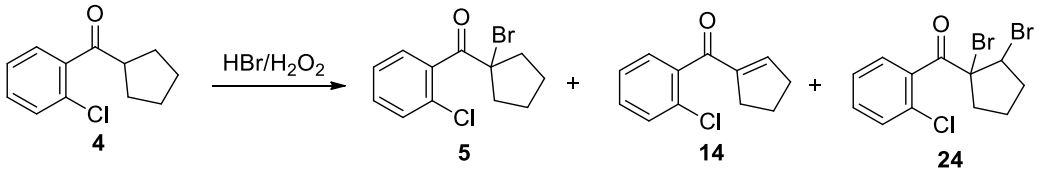
Scheme 7. The Proposed Formation Mechanism of Impurity **24**



The workup process involved the addition of saturated sodium sulfite solution to quench the unreacted hydrogen peroxide, followed by the addition of n-hexane for

extraction. The residual oxidant and hydrogen bromide were removed from n-heptane after washing three times with saturated sodium sulfite solution followed by concentration of the organic phase. The brown liquid **5** was obtained in 98.6% purity with the yield of 96.8%. The minor quantities of **14**, **24** and the residual **4** were removed in the next step. The hydrolytic impurity of **25** was detected by HPLC to be less than 0.4%, and it could be convert to the next intermediate α-hydroxyimine **6**.

Table 3. Screening of Reaction Stoichiometry for the Bromination Reaction [a]



Entry	equivalence ratio	*t*(h)	HPLC [b]			
	4:HBr:H_2O_2		**4**	**5**	**14**	**24**
1	1:1.0:1.0	20	14.2%	84.2%	1.1%	0.5%
2	1:1.5:1.5	20	5.2%	92.9%	1.1%	0.8%
3 [c]	1:1.5:1.5	3	0.5%	98.7%	0.6%	0.2%

[a] Reaction temperature: 10 °C ~ 60 °C, solvent-free, 200 rpm, H_2O_2 dripping slowly. [b] Only peak areas (%) of **4**, **5, 14** and **24** were integrated on HPLC. [c] 400 rpm, temperature: 70 °C ~ 80 °C

Preparation of α-Hydroxyimine (6)

The α-bromo ketone **5** in the treatment with excessive liquid methylamine at low temperature -40 °C afforded the α-hydroxyimine **6** [12f, 13]. Following the above conditions, a more abundant impurities with the molecular weight of 237.7 was detected at a level of approximate 30% on LC-MS (**Table 4**, entry 1). The impurity structure was confirmed as amino ketone **27** by HRMS, 1D NMR and 2D NMR. The reaction mechanism reported by Stevens [12f] gave us the direction of the optimization. The methylamination conducted in liquid methylamine containing a molar equivalent of O^{18} enriched water, and the α-hydroxyimine **6** demonstrated no measurable incorporation of the O^{18} label. The evidence supported the intramolecular nature of the oxygen migration through the epoxyamine **28** as an intermediate (**Scheme 8**, path A). In other words, water did not play any role in the reaction. Considering that 40% methylamine is more convenient to store and commercially available, liquid methylamine was replaced and the experimental results were listed in **Table 4**. Initially, the α-bromo ketone **5** reacted with 40% methylamine aqueous solution in THF at -20 °C for 24 h, and the conversion was less than 40% presumably due to the low temperature (**Table 4**, entry 2). Subsequently, the reaction was completed when temperature increased to 25 °C (**Table 4**, entry 3). However, two impurities were generated, one of which was the substituted impurity **27** at a level of approximate 25.3% on HPLC, and the other one was **25** with the content of 10.8%, caused by the hydrolysis of bromide in alkaline aqueous solution. Moreover, the hydrolytic impurity **25** showed a trend of increasing at

early timepoints and then decreasing, due to the nucleophilic addition of the methylamine to the carbonyl group despite the presence of water. This is another path to get the target product **6** (**Scheme 8** path B). From the above study, the reaction mechanism of methylamination with methylamine aqueous solution was put forward in **Scheme 8.**

Scheme 8. Two Paths of Methylamination in Methylamine Aqueous Solution (Curved arrow only for Path A)

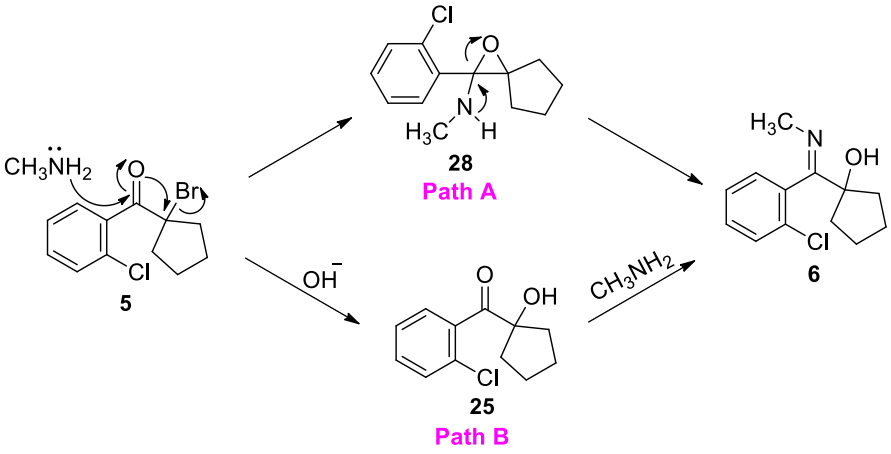
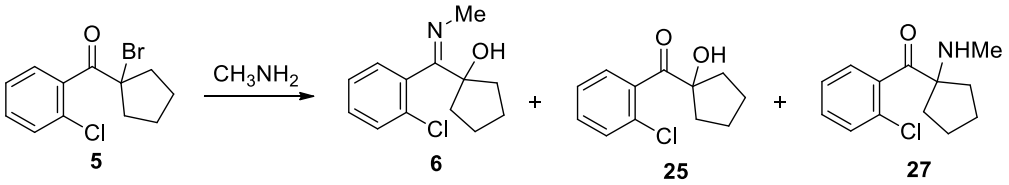


Table 4. Preparation of **6** under Various Temperature and Solvent [a]



Entry	T (°C)	Solvent	HPLC(%) [b]			
			5	**6**	**25**	**27**
1[c]	-40	-	0.2	67.2	0	32.6
2[d]	-20	THF	60.8	29.9	0.9	8.4
3	25	THF	1.1	62.8	10.8	25.3
4	25	CH_2Cl_2	0.8	41.7	8.6	48.9
5	25	-	1.6	77.2	4.3	16.9

[a] **5** react with excess methylamine, 24 h; [b] HPLC purity of the reaction mixture, only peak areas (%) of **5, 6, 25** and **27** were integrated. [c] liquid methylamine; [d] 40% methylamine aqueous solution for entries 2-5.

According to the above analysis, the next optimization direction was to avoid the generation of **27**, because it could not be converted into **6**. The reaction was then carried out in different solvents. Interestingly, the impurity **27** content was formed at the lowest levels in solvent-free condition, followed by THF, but formed at the highest levels in water-insoluble CH_2Cl_2 (**Table 4**, entries 3-5). The lipid-soluble **5** and most

methylamine will be dissolved in dichloromethane when the solvent is dichloromethane. In this case, the reaction mixture becomes oil-water two-phase and methylamine will react with **5** in the same phase. Compared with water as solvent, more methylamine will react with **5** in dichloromethane by nucleophilic substitution. It is speculated that the content of **27** was mainly affected by the concentration of methylamine interacting with **5**. Therefore, we reduced the concentration of methylamine aqueous solution, and the results showed that the amounts of **27** decreased with the decrease of the concentration of methylamine (**Table 5**, entries 1-3). As the temperature affects the selectivity of nucleophilic substitution, reaction temperature was further investigated. When the temperature reduced to 15 °C, **27** dropped to approximately 3.8% on HPLC (**Table 5**, entry 4). However, if the temperature was adjusted to 5 °C, the reaction time would be needed to be prolonged to more than 3 days for complete conversion, which was not conducive to large-scale production (**Table 5**, entry 5). Moreover, the low reaction temperature was favorable for blocking the rearrangement of the hydrolytic impurity **25** to **29**. It could be found that the content of **29** decreased as the temperature was lowered (**Table 5**, entries 3-5). The generation mechanism of **29** and the summary of all side reactions involved in methylamination were proposed as show in **Scheme 9**. According to the above experimental data, the substituted impurity **27** and the hydrolytic impurity **25** could be controlled to less than 3.0% under the synergistic action of the concentration of methylamine and the reaction temperature (**Table 5**, entry 6). The optimum reaction conditions for the preparation of α-hydroxyimine **6** were

determined as follows: 15% methylamine aqueous solution reacted with **5** at 15-20 °C for 48 h without solvent.

Scheme 9. All the Side Reactions Involved in Methylamination

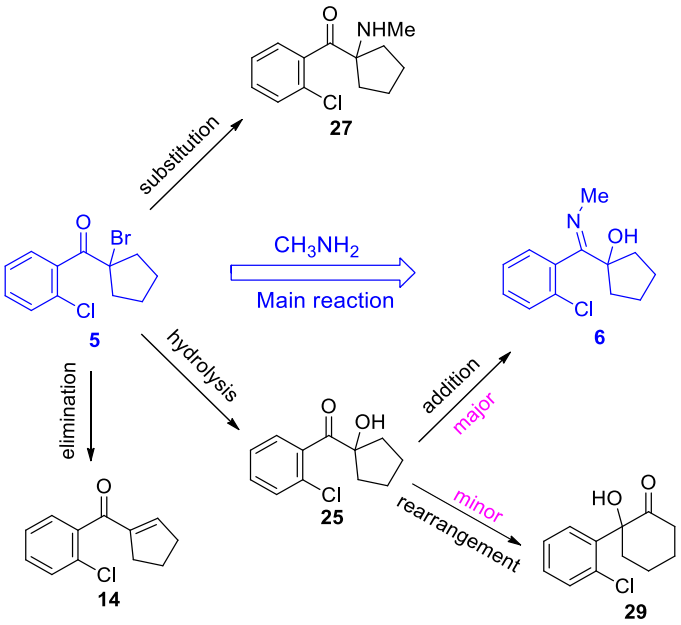
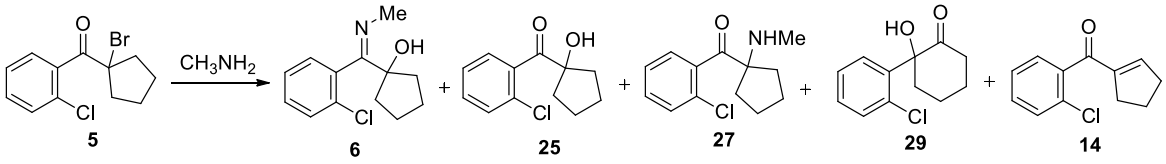


Table 5. Preparation of **6** with Various Concentration of Methylamine Aqueous Solution under Various Temperature [a].



Entry	Concentration of CH_3NH_2 (%)	T/t (°C/h)	HPLC(%) [b]				
			6	**25**	**27**	**29**	**14**
1	40	25/24	76.3	3.1	16.5	3.3	0.8

2	30	25/24	79.6	4.4	12.3	3.0	0.7
3	20	25/48	86.1	2.3	7.2	3.7	0.7
4	20	15/48	91.2	2.4	3.8	2.1	0.5
5	20	5/80	90.0	5.8	3.1	0.8	0.3
6	15	20/48	91.8	3.0	2.9	1.8	0.5

[a] Reaction condition: 15 V methylamine aqueous solution with various concentration; 400 rpm, the residue of **5** was below 1.5% ; [b] HPLC purity of the reaction mixture.

Due to the insolubility of 6 in water, the precipitates would generate during the reaction processing, and desired precipitates was easily filtered from the reaction mixture. Little remaining product and most of the impurities were detected in the mother liquors by HPLC. The workup procedure was simpler and more efficient than the extraction operation as reported by the literature. After drying under vacuum at 35 °C for 8 h, the obtained solid was an HCl salt in ethyl acetate to give **6** hydrochloride. The impurities **14**, **25**, **29** and most of the impurity **27** remained in ethyl acetate. In order to obtain a higher purity of **6** and reduce the purification pressure of the target product, **6** hydrochloride was then reslurried by THF under reflux temperature for 2 h. The off-white solid with 99.0% purity was obtained. The hydrolytic impurity **25** was 0.08% and the substituted impurity **27** was less than 1.0%.

Rearrangement of α-Hydroxyimine Hydrochloride (*rac*-1)

The thermal rearrangement, also known as ring-expansion reaction, was carried out in ethyl benzoate or decalin at 170-180 °C for 0.5-1.0 h [12-13]. Under the above conditions, the obtained product was a black gray precipitate, which indicated the ketamine was carbonized at such high temperature. What was worse, the hydrolytic impurity **25** from α-hydroxyimine **6** was detected at approximately 25% on HPLC (**Table 6**, entry 1), resulting from a small amount of moisture from **6** and solvent in the reaction mixture. Because trace amount of water is enough to cause the hydrolysis of imine hydrochloride at high temperature, leading to a low yield of rearrangement (70%). Therefore, it was pressing and necessary to seek a solution to the carbonization and hydrolysis of imine hydrochloride salt. When the temperature reduced to 140 °C, the rearrangement was conducted smoothly with the time extension to 18 h (**Table 6**, entry 2). Although the carbonization was improved and obtained the grey solid, the hydrolytic impurity **25** did not decreased. Subsequently, a rearrangement with free base of **6** was attempted to avoid hydrolysis. However, the conversion and yield were much lower than that of hydrochloride, which was consistent with what was reported [12d].

Based on the acid catalytic mechanism of the reaction (**Scheme 10**), the frequently-used Lewis acid aluminum chloride ($AlCl_3$), was selected to catalyze the thermal rearrangement and absorb the trace moisture in the reaction mixture. The experimental results were roughly the same as expected and summarized in **Table 6**. When the hydrochloride salt of **6** was subjected to the thermal rearrangement at 140 °C with 0.1 equivalent $AlCl_3$, **25** was reduced to 2.1% and the reaction time was shortened

to 2 h from 18 h. However, a new impurity with the same molecular weight as **25** was detected at approximately 8.6% on HPLC (**Table 6**, entry 3). It was presumed that **25** was rearranged to the impurity **29** at the presence of $AlCl_3$. When the amount of $AlCl_3$ was 1.5 equivalent of the moisture which was determined through Karl Fischer Moisture Titrator in **6** hydrochloride and solvent, the content of **29** reduced to 3.3% under the nitrogen atmosphere. The lower reaction temperature was still expected to reduce risk in manufacturing scale-up. To our delight, the thermal rearrangement still could be successfully completed in 5 h at 125 °C, but when the temperature decreased to 110 °C, there was still 5.6 % residual when the reaction time prolonged to 24 h. Ultimately, the optimized process was as follows: under a nitrogen atmosphere, **6** hydrochloride and $AlCl_3$ (1.5 equiv of the moisture) reacted in ethyl benzoate at 125 °C for 5-6 h. The critical process parameter, the moisture content in the solvent and **6**, was lower than 150 ppm and 2000 ppm respectively.

Scheme 10. The Proposed Mechanism of the Thermal Rearrangement

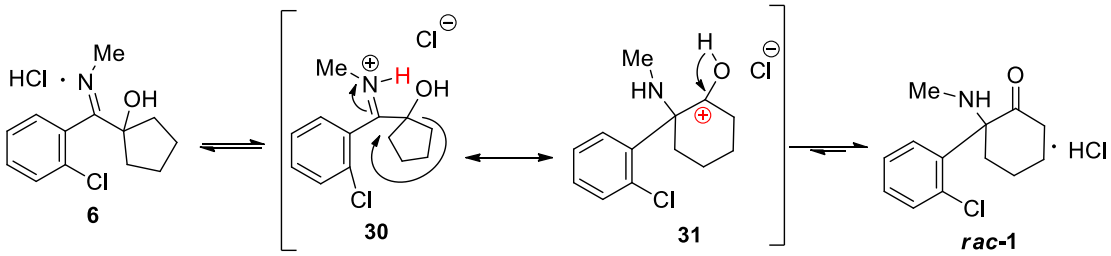
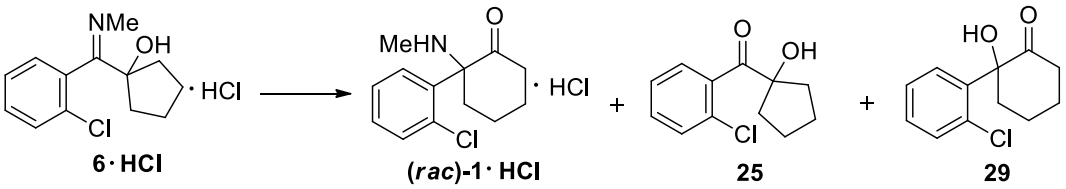


Table 6. The Thermal Rearrangement with $AlCl_3$ under Various Temperature [a]



Entry	Catalyst	*T/t* (°C/h)	HPLC (%) [b]			
			6	**1**	**25**	**29**
1	-	180/2	-	74.4	25.3	0.3
2	-	140/18	0.1	77.1	22.7	0.2
3[c]	$AlCl_3$	140/2	0.1	89.3	2.1	8.6
4[d]	$AlCl_3$	140/2	-	95.7	1.0	3.3
5[d]	$AlCl_3$	125/5	0.1	95.5	0.7	3.8
6[d]	$AlCl_3$	110/24	5.6	91.2	0.4	2.8

[a] Reaction conditions: 0.1 g/mL α-hydroxylimine hydrochloride **6** in ethyl benzoate under a nitrogen atmosphere; [b] Only peak areas (%) of **5**, **25**, **29** and **1** were integrated on HPLC; [c] 0.1 equivalent $AlCl_3$; [d] 1.5 equivalent $AlCl_3$ (the moisture in **6** and solvent).

Afterwards, the solution was cooled to room temperature and then cyclohexane was slowly added. The resulting precipitates were filtered from the mixture and washed with cyclohexane, achieving the 99% chemical purity on HPLC. Most of the impurities

25, **27** and **29** remained in the mother liquors detected by HPLC (**25**<0.1%, **27**<0.3%, **29**<0.2% in crude ketamine).

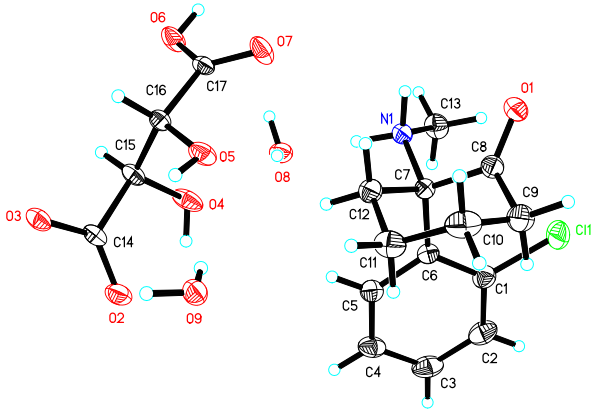
Preparation of Esketamine Hydrochloride (*S*-1).

According to the relevant research, the commercially available and inexpensive L-(+)-tartaric acid was finally chosen as the chiral resolution agent and performed in a mixture of acetone and H_2O [10]. Subsequently, different proportions of acetone and H_2O were screened, and the yield of resolution was up to 46% (lit [10a] 45%) when the chiral resolution was performed in the mixture acetone and H_2O at 15:1, and the chiral purity of tartrate **11** was 99.5% with gradient cooling process.

Acetone was removed from the mother liquors after the resolution and then the solid enriched with (*R*)-isomer was obtained after basification with NaOH aqueous solution. What puzzled us was that the ratio of the (*R*)-**1** and (*S*)-**1** displayed in chiral HPLC was *R*: *S*=85:15. However, the content of (*S*)-isomer in mother liquor should be at most 8% according to the 46% yield. In order to make the contradiction clear, the resulting tartrate was subsequently alkalized by sodium hydroxide aqueous solution and extracted by dichloromethane, yielding only 41%, which had a big difference with the resolution yield (46%). Many factors were investigated, and eventually SCXRD gave us the final answer that the crystalline unit cell of (*S*)-ketamine tartrate contains two water molecules (cultured from acetone/ H_2O, **Figure 1**). At present, there is no information about the crystal water of (*S*)-ketamine tartrate through an extensive

literature review. This is the first report that the (*S*)-ketamine tartrate is a dihydrate, which makes the molecular weight of dihydrate is corrected to 423 but not 387 reported in the literature [10c]. According to the definite molecular weight 423, the resolution yield was 41%, which is consistent with the yield of alkalization of the resulting (*S*)-ketamine tartrate with sodium hydroxide.

Figure 1. The SCXRD of Tartrate of Esketamine



Initially, the direct conversion of tartrate to hydrochloride in 5V isopropanol was considered, but the experimental result showed that the yield was only 85% which might be caused by the free water in isopropanol and the crystalline water in tartrate. Finally, the conventional process was adopted, where the tartrate was alkalized with diluted sodium hydroxide aqueous solution to get the free base and further formed a salt with hydrochloric acid in ethyl acetate to obtain the desired crude drug substance. The purification of (*S*)-**1** hydrochloride via a recrystallization process was performed in the mixture of acetone and water at the ratio of 7:1 (v/v) and a good yield (~80%) of drug substance with ICH-grade quality was obtained (99.8% purity and 99.9% e.e.).

The physical properties and the structure of purified (*S*)-**1** hydrochloride was characterized by DSC, TGA, EA, HRMS, NMR and SCXRD, and all the date were available in the Supporting Information.

Recycling of the Unwanted (*R*)-1 Enantiomer

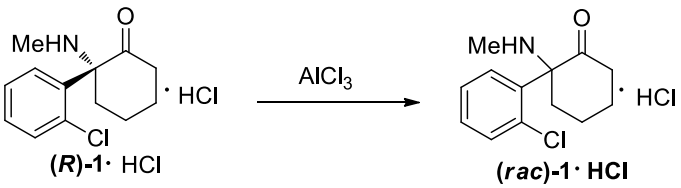
The unwanted (*R*)-**1** isomer lost in the resolution mother liquors not only lowers the total yield of the route, but also produces a large amount of waste. However, the defects can be overcome adequately supposing that the conversion of (*R*)-**1** isomer back to the racemic **1**. Herein, the recycling of the unwanted (*R*)-**1** enantiomer from the resolution mother liquors was studied. According to our previous study (the unpublished work is under revision at present, Manuscript ID: op-2019-00436u.R1), the catalytic efficiency of several frequently-used Lewis acids are arranged as follow: $AlCl_3 \approx MgCl_2 > FeCl_3 > ZnCl_2 > BF_3 > CaCl_2$. Considering the high catalytic efficiency and removability, $AlCl_3$ was finally selected to catalyze the racemization of (*R*)-**1**.

The equivalent of $AlCl_3$ was further investigated and the results were summarized in **Table 7**. 20 mol % of $AlCl_3$ was required for the racemization of (*R*)-**1** in previous studies (entry 1). The possibility of further racemization of the $AlCl_3$ was attempted and it was observed that 10 mol % of $AlCl_3$ was not enough to afford a racemic mixture of (*R*)-**1**/(*S*)-**1** in 10 h (entry 2). To our delight, when the time was extended to 24 h, a racemic mixture of (*R*)-**1**/(*S*)-**1** = 49.5 / 50.5 was obtained. However, when reaction temperature was dropped to 130 °C with 20 mol % of $AlCl_3$, the racemization rate was

much slower compared to that at 150 °C (entry 4). The updated racemization procedure was as follows: The (*R*)-**1** hydrochloride was treated with 10 mol % of $AlCl_3$ in ethyl benzoate at 150 °C for 24 h with 99% yield. The racemized ketamine was subsequently resolved by L-(+)-tartaric acid to obtain (*S*)-**1** in 41% yield and with 99.5% e.e. With three times recycling of the (*R*)-**1**, the yield of resolution could reach to 87%, and the overall yield was up to 51.1% (14.0% without racemization). Such a concise and cost-efficient approach of the racemization could be industrially useful to recycle the waste (*R*)-ketamine into the resolution process to obtain the (*S*)-ketamine.

Table 7. Optimization of aluminum chloride and temperature for the (*R*)-**1** racemization.

[a]



(*R*)-**1**· HCl (*rac*)-**1**· HCl

Entry	equiv ($AlCl_3$)	*T*/*t* (°C/h)	(*R*)-**1**/(*S*)-**1** (%)[b]	**6** (%)[c]
1	0.2	150/10	49.8/50.2	0.4
2	0.1	150/10	65.2/34.8	10.9
3	0.1	150/24	49.5/50.5	0.2
4	0.2	130/10	81.2/18.8	30.5

[a] Reaction conditions: 0.1 g/mL (*R*)-1 hydrochloride (98.5% e.e) in ethyl benzoate; [b] Measured by HPLC on a Chiralpak OD-3 column; [c] Measured by HPLC on a Waters X-Bridge C18 column, only peak areas (%) of **6** and **1** were integrated.

Control Strategy and Impurity Limit of Process Related Impurity in Esketamine

The optimized process could not only be industrially scalable but also be quality controllable. The process parameters were established and improved well as above described. The control strategy and impurity limit of process related impurities were proposed, as shown in **Table 8**.

Table 8 Control Strategy and Impurity Limit of Process Related Impurity in Esketamine

Compounds	Impurity content [a]	Control strategy and results	Impurity limit
4	**14** (1.5%)	Purification by vacuum distillation	**14** ≤ 0.5%;
	15 (0.3%)		**15** ≤ 0.3%;
	17 (0.4%)	**14** ≤ 0.4%; **15** ≤ 0.1%;	**17** ≤ 0.3%;
	20 (5.8%)	**17** ≤ 0.1%; **20** ≤ 0.8%;	**20** ≤ 1.0%;
	22 (2.3 %)	**22** ≤ 0.5%;	**22** ≤ 0.5%;
6	**4** (0.1%)	(1) Salt-forming process	**4** ≤ 0.1%;
	5 (0.5%)		**5** ≤ 0.1%;

	14 (0.3%) **25** (0.8%) **27** (1.4%) **29** (0.1 %)	**4** (ND [b]); **5** (ND); **14** (ND); **25** ≤ 0.3%; **27** ≤ 1.0%; **29** (ND) (2) THF reslurry **25** ≤ 0.3%, **27** ≤ 1.0%	**14** ≤ 0.1%; **25** ≤ 0.5%; **27** ≤ 1.0%;
Ketamine	**6** (0.08%) **25** (0.02%) **27** (0.24%) **29** (0.11 %) Ethyl benzoate (0.9 %)	Recrystallized with acetone/H_2O: **6** (ND); **25** (ND); **27** ≤ 0.03%; **29** (ND); Ethyl benzoate (ND)	**6** ≤ 0.1%; **25** ≤ 0.1%; **27** ≤ 0.1%; **29** ≤ 0.1%; Ethyl benzoate ≤ 0.1%
Esketamine	(*R*)-**1** (0.45 %)	Recrystallized with acetone/H_2O	(*R*)-**1** ≤ 0.1%

[a] Content assay of impurities using peak area normalization method; [b] Not detected on HPLC.

CONCLUSION

In conclusion, a cost-effective, recoverable, and industrially scalable synthetic process for Esketamine, has been developed and significantly optimized. Throughout the synthetic route, common and inexpensive reagents were used. The preparation of

intermediate **4** was employed Nenitzescu Reductive Acylation reaction and the reaction mechanism combined with impurities were explored clearly. The bromination reaction using hydrogen bromide combined with hydrogen peroxide as a brominating reagent which has higher atomic economy and less pollution than others performs well. Subsequently, a mild procedure for the methylamination was developed and the 15% methylamine aqueous solution, more convenient in storage and market circulation, was used to replace liquid methylamine at room temperature. The impurity profile of **6** was well characterized through thorough investigation and the impurities **23**, **25**, **27** and **29** were well controlled and removed. Aluminum chloride was used not only to catalyze the thermal rearrangement of α-hydroxyimine hydrochloride, but also to reduce the generation of **25** owing to its excellent water absorption. The SCXRD disclosed that the (*S*)-ketamine tartrate is a dihydrate, whose molecular weight was corrected in view of our first discovery. The practicable process of racemizing the unwanted (*R*)-**1** isomer from the resolution mother liquors was carried out in quantitative yield with 99% purity. When the unwanted isomer was recycled three times, the overall process yield was up to 51.1% in contrast to 14.0% without racemization. In addition, the process-related impurities were characterized by HRMS and NMR, and effectively controlled or removed to obtain the Esketamine with ICH-grade quality.

Experimental Section

General. Solvents and reagents were obtained from commercial sources and used without further purification. NMR spectra were recorded on an Avance III 600 MHz

spectrometer (Bruker, Karlsruhe, Germany). The solvents used for NMR spectroscopy were $CDCl_3$ and DMSO-d_6, using TMS as the internal reference. HRMS-spectra were obtained on Bruker maXis 4G. The DSC curves were recorded and integrated with the aid of a TA Instruments DSC Q2000 apparatus. The melting points were determined by DSC analysis and correspond to the peak maximum. Optical rotations values were measured with an Anton Paar MCP 500 polarimeter at 20 °C, 589 nm (sodium ray). Thermogravimetric analysis (TGA) was performed on a TA TGA Q500 analyzer with a heating rate of 10 °C/min under a nitrogen atmosphere. Elemental analysis (EA) was performed on a Thermo Flash 2000 instrument. Single crystal X-ray diffraction (SCXRD) data were recorded on a Bruker D8 VENTURE. The moisture content was determined on Metrohm 831 KF Coulometer. Chemical purity was determined by HPLC analysis on a Dionex UItiMate 3000 chromatograph system with UV detector. Diluents for **6** and ketamine: acetonitrile (A) and 10 mM potassium dihydrogen phosphate aqueous solution (B); Diluents for **4** and **5**: acetonitrile (A) and 0.1% formic acid-water solution (B). Column: Waters X-Bridge (C18, 4.6 mm × 150 mm, 3.5 μm). Conditions: 35 °C, flow rate 1.0 mL/min, 210 nm. LC-MS was performed on an Agilent LC/MS system consisting of an Agilent 1260-LC system equipped with a single quadruple mass detector and electrospray ionization (ESI) interface (Agilent Technologies, Santa Clara, CA, USA). Chiral HPLC analysis was done on a Dionex UItiMate 3000 chromatograph at 210 nm, using a Chiralpak OD-3 column (4.6 mm ×

250 mm, 3.0 μm) at 30 °C with flow rate of 0.8 mL/min in 20.0 min with n-hexane / 2-propanol (95:5) as eluent.

Preparation of (2-chlorophenyl) (cyclopentyl) methanone (Intermediate 4). A 30-L reactor was charged with 2-chlorobenzoyl chloride **2** (1.0 kg, 5.71 mol), $AlCl_3$ (875 g, 6.57 mol), and dichloromethane (3.0 L) under an atmosphere of nitrogen. Cyclopentene (428 g, 6.28 mol) was added to the stirring mixture at −10 ~ −5 °C over 3 h, and then the mixture was stirred for another 1 h. The reaction was monitored by HPLC and deemed proceed to the next operation step when **2** was less than 10.0%. Another $AlCl_3$ (875 g, 6.57 mol) and cyclopentane (1.5 L) were added to the reactor, and then the mixture was heated to reflux for 2-3 h. The reaction mixture was cooled to 10 − 15 °C and then added slowly into water (15.0 L) and DCM (5.0 L) over 1 h. The aqueous layer was discarded, and the organic layer was washed with 15% aqueous NaOH three times. Then, the product **4** was obtained after drying with anhydrous sodium sulfate and desolventizing. The residue was purified through vacuum rectification, and the refined product **4** with high purity was obtained as light yellow liquid, which was collected at 116-120 °C (2 mmHg) (835 g, yield: 70.3%, purity >98.5%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (dd, J = 7.9, 0.9 Hz, 1H), 7.38 (dd, J = 7.5, 1.6 Hz, 1H), 7.35 (td, J = 7.7, 1.8 Hz, 1H), 7.30 (td, J = 7.4, 1.2 Hz, 1H), 3.58 (p, J = 7.9 Hz, 1H), 1.92 – 1.84 (m, 4H), 1.76 – 1.69 (m, 2H), 1.64 – 1.59 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 206.78, 140.30, 131.08, 130.66, 130.30, 128.44, 126.75,

50.97, 29.46, 26.02. HRMS m/z $[M+Na]^+$ Calcd for $C_{12}H_{13}ClNaO$: 231.0553; found: 231.0552.

Preparation of (1-bromocyclopentyl) (2-chlorophenyl) methanone (Intermediate 5). A 10 L reactor was charged with **4** (400.0 g, 1.92 mol) and 48% HBr (485.5 g, 2.88 mol) under the condition of water bath with fast agitation. 30% hydrogen peroxide solution (326.4 g, 2.88 mol) was dripped slowly to the stirring mixture. The reaction temperature was keep at 70-80 °C by controlling the drop speed, and then the mixture was stirred for another 1 h at 75 °C. The reaction was monitored by HPLC and deemed completed when **4** was less than 1.0%. The reaction mixture was diluted with n-heptane (1.5 L) and saturated sodium sulfite aqueous solution (2.0 L). After stirring for 30 min, filtered the flocs through diatomite, and extracted with n-heptane (2 × 1.0 L). Subsequently, the organic layer was washed twice with saturated sodium sulfite aqueous solution until the hydrogen peroxide was cleaned completely. Then, the combined extracts of **5** were evaporated to dryness to give the brown liquid **5** (535 g, purity >98.5%, yield: 96.8%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (dd, J = 7.6, 1.5 Hz, 1H), 7.44 – 7.40 (dd, 1H), 7.36 (td, J = 7.8, 1.6 Hz, 1H), 7.30 (td, J = 7.5, 1.0 Hz, 1H), 2.43 – 2.36 (m, 2H), 2.34 – 2.28 (m, 2H), 2.08 – 2.00 (m, 2H), 1.91 – 1.83 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.40, 138.75, 130.73, 130.44, 130.06, 128.23, 126.39, 74.20, 40.29, 23.14. HRMS m/z $[M+Na]^+$ Calcd for $C_{12}H_{12}BrClNaO$: 310.9628; found: 310.9623.

Preparation of 1-((2-chlorophenyl) (methylimino) methyl) cyclopentanol hydrochloride (Intermediate 6). 5 (530.0 g, 1.84 mol) was treated with 15% aqueous methylamine (8.0 L) at 15-20 °C (adding 4-5V ethanol can also get the expected results). The reaction was monitored by HPLC and the end point of the reaction was **25** below 2.5%. The precipitates was isolated by filtration and washed with deionized water (1.0 L) three times and then dried at 35 °C under vacuum to give crude **6** as a brown solid (396.2 g, yield 90.8%, HPLC purity 95.6%). Crude **6** dissolved in ethyl acetate (0.8 L) in a 3-L reactor. 2.0 mol/L HCl-EA (1.0 L, 1.2 equiv) was added to the clear solution slowly over 30 min. With the dropwise of HCl, the **6** hydrochloride was precipitated, and the mixture was stirred at 20 °C for 1 h. The precipitates was filtered and washed with ethyl acetate (0.5 L) and then reslurried by THF under reflux temperature for 2 h. The off-white solid was obtained after drying under vacuum at 35 °C (426.0 g, yield: 93.1%, HPLC purity 99.0%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (dd, J = 7.7, 1.5 Hz, 1H), 7.33 (ddd, J = 6.7, 6.0, 1.7 Hz, 2H), 7.08 – 7.06 (m, 1H), 3.01 (s, 3H), 1.94 – 1.91 (m, 2H), 1.78 (ddd, J = 14.9, 5.9, 3.6 Hz, 2H), 1.67 (ddd, J = 8.3, 6.4, 3.8 Hz, 2H), 1.59 (ddd, J = 9.0, 7.9, 3.1 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.99, 133.97, 132.08, 129.89, 129.81, 128.94, 126.60, 84.29, 39.34, 38.22, 37.90, 23.53, 23.38. HRMS m/z $[M+H]^+$ Calcd for $C_{13}H_{17}ClNO$: 238.0999; found: 238.0996.

Preparation of 2-(2-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride (racemic ketamine). The moisture content of **6** hydrochloride and ethyl benzoate was about 1800 ppm and 110 ppm, respectively. A 10 L reactor was charged with α-

hydroxyimine hydrochloride **6** (350.0 g, 1.28 mol), $AlCl_3$ (11.3 g, 0.085 mol), and ethyl benzoate 3.5 L under an atmosphere of nitrogen. The mixture was stirred for 5 h at 125 °C. The reaction was monitored by HPLC and deemed complete when **6** was less than 0.5%. The reaction mixture was cooled to 15-20 °C slowly, and 2.0 L n-hexane was added in the mixture. After stirring for 1 h, the solid product was isolated by filtration, washed with cyclohexane (1.0 L), and then dried under vacuum at 50 °C to yield the crude product as an off-white solid (327.6 g, yield: 93.6%, HPLC purity 98.7%). Crude *rac*-**1** hydrochloride and acetone (2.85 L) were placed in a 5 L reactor and heated to reflux for 20 min. Deionized water (0.41 L) was added to the suspension slowly until it was dissolved, and then slowly cooled to 45 °C and crystal seeds were introduced to the solution, stirred at this temperature for 2 h. The suspension was cooled to 0 °C by gradient cooling. The precipitate was filtered, washed with acetone (0.6 L) and then dried at 50 °C under vacuum to yield racemic ketamine hydrochloride as a white flour solid (263.0 g, yield: 80.3%, HPLC purity 99.8%). Mp 265.04 °C. Anal. Calcd for $C_{13}H_{17}Cl_2NO$: C, 56.95; H, 6.25; N, 5.11. Found: C, 56.87; H, 6.27; N, 5.13. ^{1}H NMR (600 MHz, DMSO) δ 7.94 (d, J = 6.7 Hz, 1H), 7.65 – 7.56 (m, 3H), 3.30 (s, 1H), 2.54 – 2.51 (m, 1H), 2.44 (td, J = 12.6, 5.9 Hz, 1H), 2.34 (q, J = 6.0 Hz, 1H), 2.21 (s, 3H), 2.02 (d, J = 12.2 Hz, 1H), 1.93 (t, J = 13.6 Hz, 1H), 1.80 (d, J = 14.1 Hz, 1H), 1.72 – 1.62 (m, 1H), 1.54 – 1.45 (m, 1H). ^{13}C NMR (151 MHz, DMSO) δ 207.26, 134.42, 132.62, 132.11, 128.73, 71.93, 40.00, 36.99, 29.67, 28.08, 21.55. HRMS m/z $[M+H]^+$ Calcd for $C_{13}H_{17}ClNO$: 238.0999; found: 238.0996.

Preparation of (*S*)-2-(2-chlorophenyl)-2-(methylamino) cyclohexanone tartrate (Esketamine tartrate, 11). Racemic ketamine hydrochloride (240.0 g, 0.88 mol) was dissociated with 1N NaOH aqueous solution (1.0 L) to the pH = 10 - 11 and the precipitate was filtrated, then washed with deionized water (500 mL), and dried at 50 °C under vacuum to give *rac*-**1** base as a white solid (205.1 g). L-tartaric acid (71.5 g, 0.47 mol) were dissolved in a mixture of acetone (1920 mL) and water (128 mL) by heating at reflux for 30 min and became clear before being allowed to naturally cool to 55-58 °C. Crystal seeds were introduced to the solution, and the mixture was stirred at 55 °C for 2 h and then the suspension was cooled to room temperature at approximately 5 °C/h. The resulting slurry was stirred overnight. The white solid was filtered, washed with cold acetone (2 × 300 mL). The mother liquor enriched (*R*)-**1** was concentrated under reduced pressure and then alkalized with 1 N NaOH solution to give the precipitate of (*R*)-**1** for the recovery operation. The diastereomerically pure tartrate was dried at 50 °C under vacuum overnight to yield 151.7 g (optical purity >99.5%, HPLC purity >99.5%, yield: 41.5%), $[\alpha]_D^{20}$ +65.8 (*c* 1.0, H_2O). (lit., [10a] $[\alpha]_D^{20}$ +68.8 (*c* 2.0, H_2O)).

Preparation of (*S*)-2-(2-chlorophenyl)-2-(methylamino) cyclohexanone hydro chloride (Esketamine hydrochloride, (*S*)-1). Esketamine tartrate (150.0 g, 0.35 mol) was dissociated with 1N NaOH aqueous solution (500 mL) to the pH = 10 - 11 and the precipitates was filtrated, then washed with deionized water (500 mL), and dried at 50 °C under vacuum to give Esketamine base as a white solid (82.7 g). Esketamine base

was dissolved in ethyl acetate (0.15 L) and 2.0 mol/L HCl-EA (0.2 L) was added to the clear solution slowly over 20 min. With the addition of HCl, the target product was precipitated, then the suspension was stirred at 20 °C for 1 h. The precipitates was filtered and washed with ethyl acetate (0.2 L) and then dried under vacuum at 40 °C to give crude (*S*)-**1** hydrochloride (94.8 g). Crude (*S*)-**1** and acetone (0.83 L) were placed in a 2 L reactor and heated to reflux for 20 min. Deionized water (0.12 L) was added to the suspension slowly over 30 min to get the clear solution. The solution was slowly cooled to 45 °C and crystal seeds were introduced to the solution, stirred at this temperature for 2 h. The suspension was cooled to room temperature at approximately 5 °C/h. The solid was filtered and washed with acetone (0.5 L) and then dried at 50 °C under vacuum to yield Esketamine hydrochloride as a white flour solid. (76.7 g, yield: 79.0%, optical purity >99.9%, HPLC purity >99.8%). Mp 273.54 °C. Anal. Calcd for $C_{13}H_{17}Cl_2NO$: C, 56.95; H, 6.25; N, 5.11. Found: C, 56.83; H, 6.25; N, 5.09. $[\alpha]_D^{20}$ +91.522 (*c* 1.0, H_2O). ^1H NMR (400 MHz, MeOD) δ 8.05 – 7.91 (m, 1H), 7.67 (qd, J = 5.6, 3.4 Hz, 3H), 4.87 (s, 2H), 3.53 – 3.38 (m, 1H), 2.64 – 2.52 (m, 2H), 2.43 (s, 3H), 2.21 – 2.12 (m, 1H), 2.02 – 1.91 (m, 2H), 1.89 – 1.71 (m, 2H). ^{13}C NMR (101 MHz, MeOD) δ 206.45, 134.04, 132.07, 131.50, 131.48, 127.96, 127.42, 71.86, 38.98, 35.75, 29.21, 26.29, 20.97. HRMS m/z $[M+H]^+$ Calcd for $C_{13}H_{17}ClNO$: 238.0999; found: 238.1002.

Racemization of (*R*)-1 hydrochloride. The resolution mother liquors enriched (*R*)-**1** was distillated under reduced pressure to remove acetone and then dissociated with 1

N NaOH solution. The obtained solid after dried at 50 °C under vacuum overnight was salted with EA-HCl in ethyl acetate to get the enriched (*R*)-**1** hydrochloride with 99.5% chemical purity and 85.1% chiral purity. A solution of the enriched (*R*)-**1** hydrochloride (135.0 g, 0.49 mol) in ethyl benzoate (1.3 L) was stirred with $AlCl_3$ (6.6 g, 10% mol) at 150 °C. The racemization process was monitored by chiral HPLC analysis. After (*R*)-**1** was found to be fully racemized, the reaction mixture was cooled to room temperature and then cyclohexane (650 mL) was added to make the precipitation completely. The racemic mixture of (*R*)-**1**/(*S*)-**1** (49.5%/50.5%) as an off-white solid (138.3 g) in quantitative yield with 99.5% chemical purity. The obtained racemic ketamine was alkalized with 2 N NaOH aqueous solution (2.0 L) to the pH = 11-12 and the mixture was stirred for 2 h to make $AlCl_3$ convert to $NaAlO_2$. Subsequently, the precipitates was filtrated, washed with deionized water, and then dried at 50 °C under vacuum. The racemized ketamine was subsequently resolved by L-(+)-tartaric acid to obtain (*S*)-**1** in 41% yield and with 99.5% e.e.

Associated Content

Supporting Information

Analytical spectrograms and data of compounds **4**, **5**, **6**, **Ketamine** and **Esketamine**; SCXRD of **Esketamine tartrate (11)**, **Esketamine hydrochloride** and impurity **29**; HPLC and Analytical spectrograms of the **racemized Ketamine**; HPLC, HRMS and

NMR spectra of impurities **14**, **15**, **17**, **21**, **22**, **24**, **25**, **27**, **29**. Complete Reference for Gaussian 09, Computational Methods and M06 Geometries for carbocation **13**, **16** and **Transition States**.

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