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Article

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A Process for (*S*)-Ketamine and (*S*)-Norketamine via Resolution Combined with Racemization

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For Table of Contents Only

Keywords

(*S*)-Ketamine; (*S*)-Norketamine; Depression; Novel Process; Racemization

Abstract

A concise, recyclable and efficient process is presented for the preparation of (*S*)-ketamine (esketamine, (*S*)-**1a**) via classic resolution combined with the recycling of undesired isomer. A commercially available ketone **2** as starting material, this procedure features three steps including (1) an unique hydroxylation-ring expansion rearrangement, (2) a mild amination via methanesulfonate and (3) a chiral separation using *L*-(+)-tartaric acid. The three simple steps are all performed in mild conditions and (*S*)-**1**a tartrate is obtained in 99.5% ee without recrystallization. Subsequently, the racemization of the unwanted (*R*)-**1a** remained in resolution mother liquor was performed in the presence of a Lewis acid in quantitative yield with >99.0% chemical purity. This original and economical process afforded esketamine in 67.4% (28.9% without racemization) overall yield with two times recycling of the mother liquor without column purification. In addition, this procedure can also be applied to the preparation of (*S*)-norketamine, which is a safer potential antidepressants.

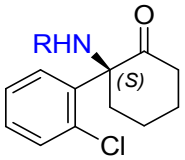
Introduction

Ketamine, (±)-2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone (**1a**), was first developed as an anesthetic in 1962 and started to be applied clinically in 1965[1]. However, ketamine was designated as a scheduled drug due to the strong dissociative side effects of psychotic symptoms (e.g., hallucination and delusion) and potential drug

addiction.

In recent times, ketamine has elicited tremendous excitement, since it has presented rapid and sustained antidepressant efficacy for treating major depressive disorders[2-5]. Depression is a common neurological disorder and has become a major public health problem, affecting about 320 million people worldwide at some point in their lives[6-7]. Unfortunately, several weeks even months are required for current antidepressants to exert their drug efficacy, and there are about 30% treatment-resistant patients for whom the antidepressants are ineffective[6]. Ketamine, on the contrary, is effective within hours (in as little as half an hour) after a single administration, and sustains the antidepressant effects for 7-10 days[1, 8]. The racemic ketamine, as the N-methyl-D-aspartate (NMDA) receptor antagonist, contains equal amounts of (*R*)-ketamine and (*S*)-ketamine ((*S*)-**1a**, Scheme **1**). Compared with *(R)*-ketamine, (*S*)-ketamine displays 3-4 times greater affinity for NMDA receptor, thus potentially allowing for lower dosages[9]. Recently, esketamine (SPRAVATO™) has been approved by FDA to treat the major depression in adults, which represents a significant milestone for the depression treatment in decades[10].

Scheme 1. Structures of (*S*)-Ketamine and (*S*)-Norketamine



R=CH_3, (*S*)-Ketamine (**1a**)

R=H, (*S*)-Norketamine (**1b**)

At present, the preclinical data[11] indicate that the (*S*)-norketamine ((*S*)-**1b**, Scheme **1**), a major metabolite of (*S*)-ketamine by cytochrome P450 enzymes, exhibits a rapid

and robust antidepressant effect which is equal to (*S*)-ketamine. Interestingly, (*S*)-norketamine, due to the lower affinity for the NMDA receptor[12], shows significantly less side effects in rodents than that of (*S*)-ketamine. Thus, (*S*)-norketamine will be a safer alternative antidepressant, and notably, (*S*)-norketamine is not designated as a scheduled compound[12, 13].

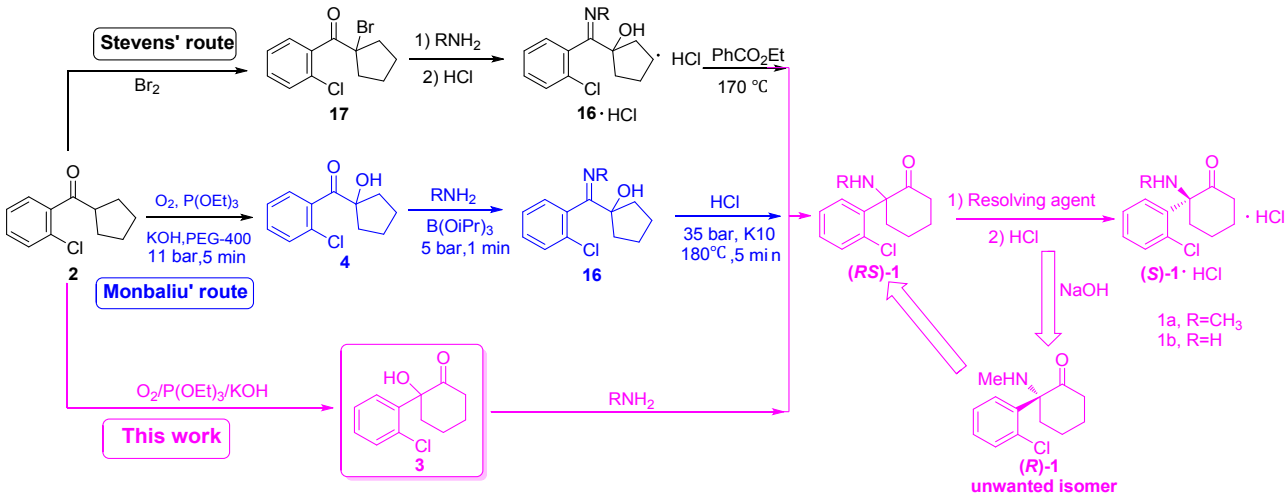
Stimulated by the stronger potency of (*S*)-ketamine for the NMDA receptor, many asymmetric synthetic routes have been reported over the years[14]. For example, the first asymmetric synthetic process of (*S*)-ketamine was reported by Kiyooka and colleagues[15]. The innovative procedure was conducted in ten steps and (*S*)-ketamine was obtained in the yield of 21% (97% ee). Unfortunately, neither the atom economy nor energy consumption is suit for large-scale production, and the utilization of excessive chiral BINAL-H catalytic agent (3.4 equiv), and ozone may be inconvenient for industrialization. Another route with similar idea (the cyanate-to-isocyanate rearrangement) was put forward by Chen and colleagues in 2019[16]. The highlight of this method was the construction of the desired quaternary stereocenter of (*S*)-ketamine using Overman rearrangement. This optimized procedure was indeed more concise and efficient than Kiyooka's and (*S*)-ketamine was obtained with high chiral purity (>99%) in 49% overall yield. Moreover, hydrolysis of the isocyanate functional group led to (*S*)-norketamine. Toste[17a] reported a three steps process, which afforded the (*S*)-ketamine and (*S*)-norketamine in 30% overall yield (99% ee) using di-tert-butyl azodicarboxylate to construct the stereocenter. A complex chiral organophosphorus ligands, the preparation of which required several steps were needed for the key step of

this route. Additionally, the staring material, *o*-chlorophenyl cyclohexanone, is not commercial and prepared in column chromatography with only 59% yield[17]. Lately, using (*S*)-tert-butanesulfinamide as the chiral auxiliary, the desired chiral center of (*S*)-ketamine was installed with the unsatisfactory 75% ee[18]. (*S*)-Norketamine synthesized by using asymmetric synthesis strategy was first reported by Biermann and co-workers[19] via Sharpless epoxidation, Ritter reaction and Jones oxidation. Unfortunately, the key step of SAD gave the unsatisfactory 87% ee, and the Ritter amination was performed with a low yield (47%) due to the poor selectivity of two hydroxyl groups. Even though the above asymmetric synthesis of (*S*)-ketamine have acquired a certain success, an efficient and scalable synthesis to enantiopure (*S*)-ketamine and (*S*)-norketamine was desired. In view of *rac*-**1a** and *rac*-**1b** are common pharmaceutical formulations, classical resolution [20] of the inexpensive racemate (±)-**1** remains a better choice to prepare (*S*)-**1a** and (*S*)-**1b** from the industrial standpoint.

Three synthetic routes of racemic ketamine and norketamine were reported in the literature. The original synthetic route was reported by Stevens[21] using commercially available ketone **2** as the starting material (**Scheme 2**). This concise procedure including three steps of bromination, imination and thermal rearrangement. However, there are some disadvantages in this route, such as low atomic economy (copper bromide and excessive liquid methylamine) and harsh reaction conditions (-40 °C and 180 °C) Recently, Zhang and colleagues[23] reported a new strategy to synthesize (±)-**1** using the uncommercial *o*-chlorophenyl cyclohexanone as the starting material, which was next

subjected to direct nitration utilizing excessive ceric ammonium nitrate ($(NH_4)_2Ce(NO_3)_6$). Unfortunately, the nitration step was conducted in dichloroethane with a low isolated yield (51%) and consequently resulted in an unsatisfactory total yield (25%). More recently, another environment-friendly procedure which relies on the continuous flow reactor for the preparation of (±)-**1** was reported by Monbaliu[24] (**Scheme 2**). All the three steps were carried out in ethanol, however, it is noteworthy that the thermal rearrangement reaction was performed on montmorillonite K10 at a harsh reaction condition: (35 bar, 180 °C), and the yield was only 65% which was far lower than 95% yield in kettle reactor.

Scheme 2 Synthetic Routes to (±)-1 and (*S*)-1



The routes above have some disadvantages in terms of harsh conditions, uncommercial raw materials and unsatisfactory yield. In addition, the undesired (*R*)-**1** discarded in the resolution mother liquors would lead to a low yield, and release a substantial amount of waste residue. In order to overcome the defects in the process of racemic (±)-**1** and chiral resolution, we wish to develop a newly efficient synthetic

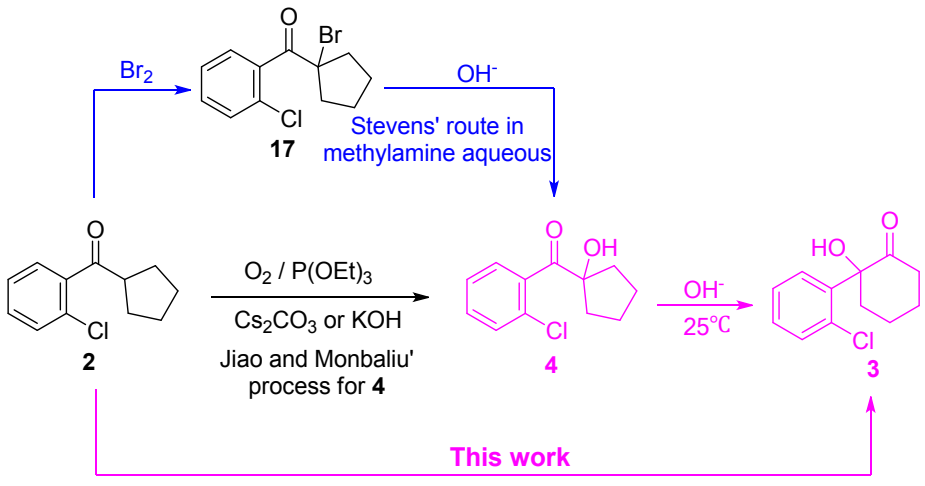
process of (*S*)-**1a** and (*S*)-**1b** via the synthesis of racemic (±)-**1** and chiral resolution combined with racemization (**Scheme 2**).

Results and Discussion

Oxidation-Rearrangement Reaction of Ketone 2

When the methylamine step in the Stevens' route was repeated with 40% methylamine aqueous solution, we found that the compound **4** would convert to compound **3** via ring expansion rearrangement under mild condition in our early works [25]. Furthermore, a brief literature [21e, 24, 26] survey revealed that the cyclic α-hydroxyketone could easily be rearranged through expanding or shrinking rings in the presence of alkali. Inspired by the above results, our initial thought was that the starting material **2** was oxidized to **4** and then **4** was rearranged to **3** under the alkalinity or high temperature. In view of both hydroxylation and rearrangement were carried out under the same alkaline condition, we envisaged that the compound **3** could be synthesized in one step starting from ketone **2** (**Scheme 3**).

Scheme 3 the Synthetic Routes to 3 Starting from 2

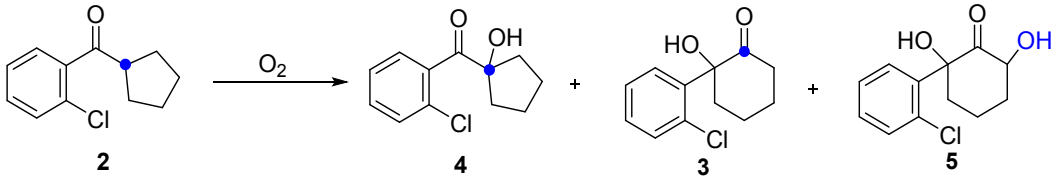


We started the work from ketone **2** which is commercially available [24] (**Scheme 3**). In various methods of preparing tertiary α-hydroxyl ketones directly from ketones, the best industrialized prospect and low toxicity procedure was disclosed by Jiao and co-worker [27] using molecular oxygen as a primary oxidizer with 20 mol% cesium carbonate (Cs_2CO_3) and an inexpensive and readily available reductant triethyl phosphite ($P(OEt)_3$) in DMSO.

The potassium carbonate (K_2CO_3), cheaper and more suitable for industrial production, but didn't work in the Jiao's report, was selected to substitute for Cs_2CO_3 (in DMSO) after analyzing literatures data. To our delight, the main product (90%) was compound **4** while 9.2% for the rearrangement product **3** (**Table 1**, entry 1). To increase the content of target product **3**, KOH with higher alkalinity was used. As we expected, the content of **3** was up to 72.7% in 1h (**Table 1**, entry 2). However, an over oxidized impurity **5** accounts for 6.4% was detected due to the newly generated product **3** still contains a carbonyl α-H, which would continue to be hydroxylated in the reaction mixture. When KOH was added into the reaction solution, the mixture was turned black brown soon. We believe the good solubility of KOH in DMSO should be responsible for this phenomenon. The short reaction time lead to the poor reaction selectivity. Subsequently, ethanol, with smaller solubility of KOH, was considered to replace DMSO. To our delight, the main product (98%) was the target ring-expanding product **3**, while the intermediate state **4** was only 1.1% in 48 h (**Table 1,** entry 3). The reaction rate was decreased and the selectivity of hydroxylation-rearrangement was improved significantly, which greatly reduced the over oxidized impurity **5**. In order to shorten

the reaction time, the temperature was raised to 50 °C by heating in oil bath, but it was found that the over oxidized impurity **5** increased to 9.6% (**Table 1**, entry 4). Moreover, other reductants such as sodium sulfite (Na_2SO_3) and sodium phosphite (Na_2PO_3) were attempted. What disappointed us was that the over oxidized impurity **5** or the residue of **2** was increased due to the poor conversion and selectivity (**Table 1**, entries 5-7). The existing experimental data demonstrated that the KOH/$P(OEt)_3$/O_2 was an appropriate system for the hydroxylation combined with rearrangement of compound **2**.

Table 1. The Oxidation-Rearrangement Reaction under a Variety of Conditions [a]



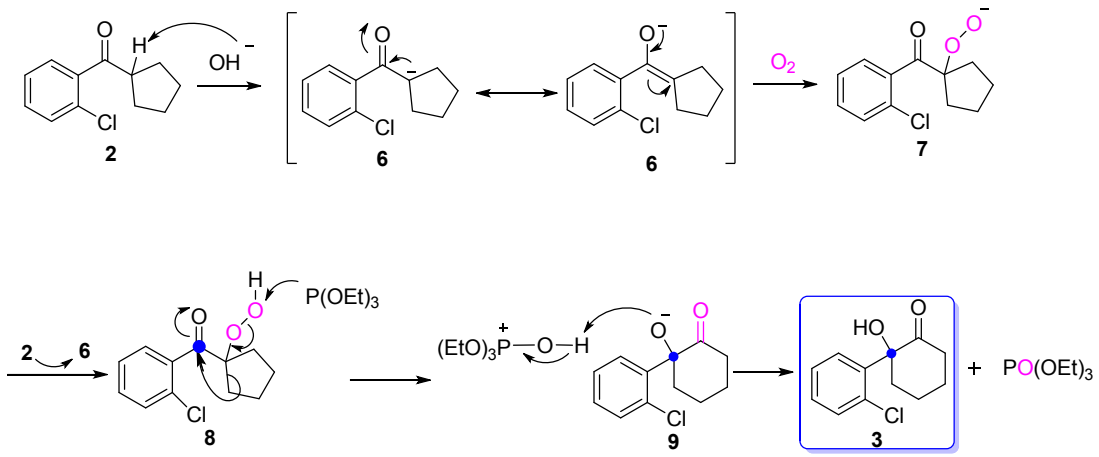
Entry	Reductants	Alkali	Solvent	*T* (°C)	t (h)	HPLC [b] (%)			
						2	**4**	**3**	**5**
1	$P(OEt)_3$	K_2CO_3	DMSO	25	35	0.1	90.7	9.2	-
2	$P(OEt)_3$	KOH	DMSO	25	1	0	20.9	72.7	6.4
3	$P(OEt)_3$	KOH	EtOH	30	48	0.2	1.1	98.0	0.7
4	$P(OEt)_3$	KOH	EtOH	50	20	0.2	1.4	88.8	9.6
5	Na_2SO_3	KOH	EtOH	30	20	0.2	0.8	34.2	64.8
6	Na_2SO_3	K_2CO_3	EtOH	30	60	66.8	5.9	14.7	12.5
7	Na_2PO_3	KOH	EtOH	30	20	30.5	1.4	25.4	42.5

[a] Reaction conditions: **2** (1.0g), reductants (1.5eq), base (1.0eq), solvent (10mL); the mixture was stirred under the atmosphere of O_2 (standard atmospheric condition); [b] only peaks of **2, 3, 4** and **5** were integrated; Heating in oil bath.

The optimal result was obtained when **2** was performed with molecular oxygen in the presence of 1.0 equiv KOH and 1.5 equiv $P(OEt)_3$ in EtOH under 30 °C for 48 h. The faint yellow solid with 99.0% purity was obtained in 83% yield after the workup procedure. The Single crystal X-ray diffraction (SCXRD) of **3** can be found in Supporting Information.

Based on the above results and related literatures [24, 27], the probable mechanism is proposed in **Scheme 4.** At first, the deprotonation of ketone **2** by KOH obtains the corresponding carbanion **6** with keto-enol tautomerism. And then, carbanion **6** reacts with O_2 to produce a peroxide anion **7**, which could acquire a proton from ketone **2** to form a peroxide **8** and reproduce another **6**. Compound **8** would subsequently be reducted by $P(OEt)_3$ and underwent ring expansion rearrangement simultaneously to give the oxygen anion **9**. Then, the desired product **3** is obtained from **9**.

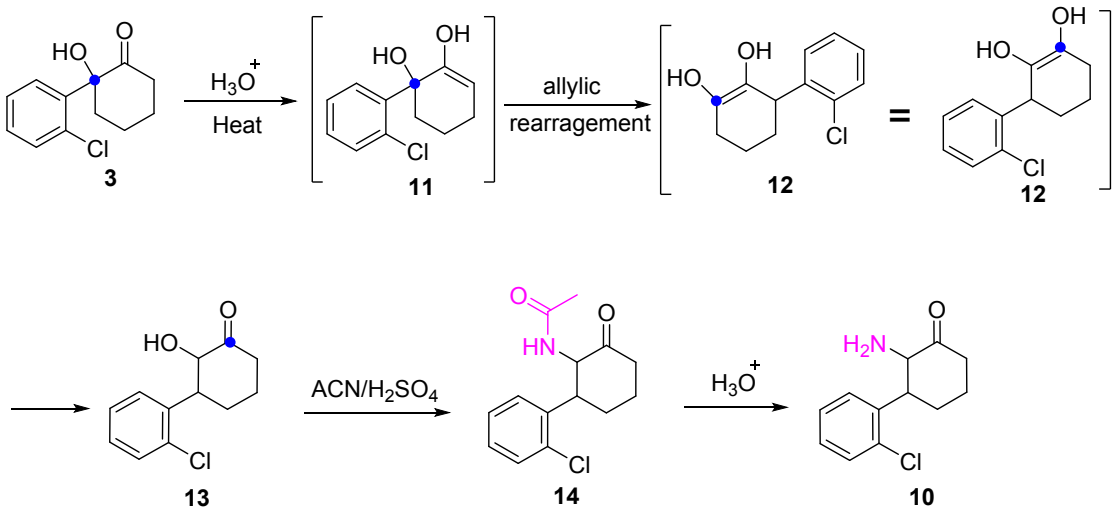
Scheme 4 the Probable Mechanism of Oxidation-Rearrangement Reaction



The preparation of ketamine and norketamine

In view of the similarity of the structure of **3** with ketamine and norketamine, our initial idea was that norketamine could be obtained by direct amination via Ritter reaction under acidic conditions. The Ritter amination of intermediate **3** was conducted in the general condition of H_2SO_4/ACN [28] followed by acid hydrolysis at 90 °C for 24 h to the norketamine. However, what puzzled us was that the obtained compound was not norketamine but its isomer **10** which was confirmed by NMR spectra (in supporting information). The literature [21d] revealed that the aryl migration and rearrangement would occur on the compounds with similar structure of **3** under acid condition. The specific rearrangement and the corresponding Ritter reaction is shown in **Scheme 5**.

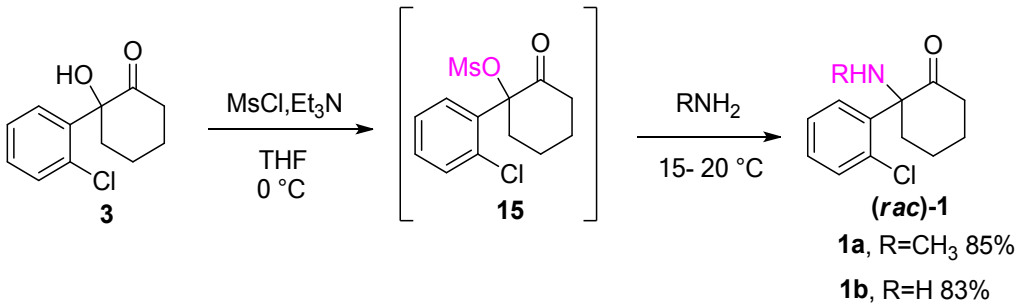
Scheme 5 the Specific Rearrangement of **3** and Corresponding Ritter Reaction



In order to synthesize norketamine and ketamine more efficiently, we explored another methods to convert hydroxyl group into amino group. Activating the hydroxyl group with sulfonate to increase its leaving ability is considered to be an efficient and simple approach to prepare amino from hydroxyl [29]. Hence, *p*-toluene sulfonyl chloride was the primary choice considering its solid properties and low toxicity. Unfortunately,

no product was obtained when the *p*-toluene sulfonyl chloride react with **3**, probably due to its large steric hindrance. To our delight, **3** can be activated via methanesulfonate strategy. Treatment of **3** with mesyl chloride (MsCl) afforded methanesulfonate **15** followed by adding excessive methylamine ethanol solution and ketamine was obtained in good yield. During the experiment, we found that the methanesulphonate **15** was very unstable and easy to eliminate, especially at high temperature. Considering the instability of **15**, there was no NMR data of the methanesulphonate, and we prepared ketamine and norketamine in one pot process as illustrated in Scheme 6: sulfonation and amination to afford ketamine with 85% unoptimized yield in 99.5% purity. When methylamine was replaced by ammonia, the norketamine was produced in the yield of 83%.

Scheme 6. Synthesis of Ketamine and norketamine via Methanesulfonate



Resolution of Ketamine and Norketamine.

Basing on the literature [20] and the previous work of our group [25, 30], the chiral resolution of racemic ketamine was carried out in acetone/water at the ratio of 15:1 with the frequently-used *L*-(+)-tartaric acid as resolution agent. The resulting tartrate of ketamine was obtained in the yield of 41% with the 99.5% chiral purity. Subsequently, the white solid esketamine base gradually

precipitated out when the tartrate alkalized by 1N NaOH aqueous solution. The products could be easily separated by simple filtration. The structure of (*S*)-ketamine was identified by HRMS, 1D NMR 2D NMR and SCXRD, and all the spectra were shown in the Supporting Information. Similarly, the resolution of norketamine was performed in $EtOH/H_2O$ by using *L*- pyroglutamic acid and the best proportion of $EtOH/H_2O$ was screened to 12:1. The (*S*)-norketamine was obtained in 42% yield with >99.5% chiral purity.

Racemization of the Undesired (*R*)-1 isomer

The route overall yield would be improved and the discharge of waste would be reduced supposing that the discarded (*R*)-**1** could be racemized and recycled. Hence, the racemization of the undesired (*R*)-**1** isomer was studied. However, since the chiral center is a quaternary carbon without hydrogen, it is a challenge for us to achieve its racemization. At present, there is no relevant literature about the racemization of (*R*)-**1**.

Although (*R*)-**1** isomer does not seem easy to achieve racemization, we have successfully converted the undesired (*R*)-**1** back to the racemic ketamine through the reversible reaction under the catalysis of a Lewis acid in our previous study [25, 30]. According to our early research, the order of catalytic capability of some commonly-used Lewis acids were as follow: $AlCl_3 \approx MgCl_2 > FeCl_3 > ZnCl_2 > BF_3 > CaCl_2$. Finally, we deemed $AlCl_3$ was the most appropriate catalyst in view of its good catalytic capacity and removability.

Further optimization of the amount of $AlCl_3$ on the racemization of (*R*)-ketamine and (*R*)-norketamine was tried (**Table 2**). In our early studies, we had found that the racemization of (*R*)-ketamine demanded 0.2 equiv $AlCl_3$ (entry 1), and only partial (*R*)-ketamine achieved the racemization (65.2/34.8) with 0.1 equiv $AlCl_3$ in 10 h (entry 2). Surprisingly, the racemization of (*R*)-ketamine was nearly completed (53.6:46.3) as the reaction time prolonged to 24h (entry 3). Moreover, we tried to lower the reaction temperature, and the racemization rate at 130 °C with 0.2 equiv $AlCl_3$ was much slower than that at 150 °C (entry 4). Similarly, (*R*)-norketamine could also be racemized completely (*R*-**1b**/*S*-**1b** (50.4/49.6)) under 150 °C with 0.2 equiv $AlCl_3$ for 15h (entry 5). The optimized procedure of the racemization was that the hydrochloride of (*R*)-ketamine or (*R*)-norketamine was heated in ethyl benzoate with 0.1-0.2 equiv $AlCl_3$ at 150°C for 10-15h.

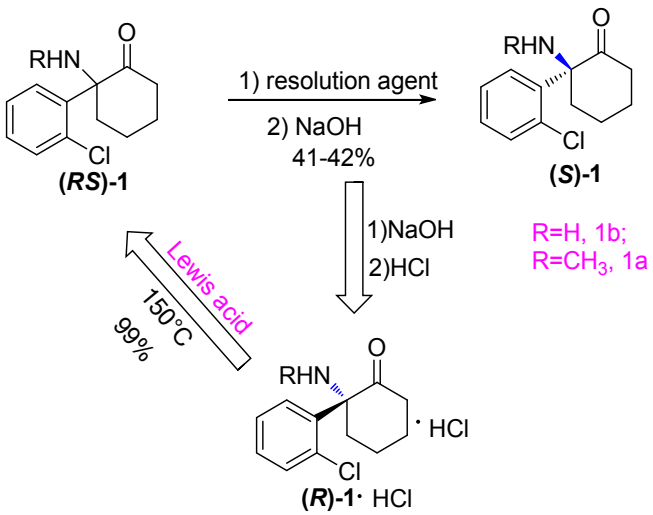
Table 2. Further Optimization for the (*R*)-1 Racemization [a]

Entry	$AlCl_3$ (eq)	*T* (°C)	*t* (h)	(*R*)-**1**/(*S*)-**1** (%)[b]
1	0.2	150	10	49.8/50.2
2	0.1	150	10	65.2/34.8
3	0.1	150	24	53.6/46.4
4	0.2	130	10	81.2/18.8

5[c]	0.2	150	15	50.4/49.6

[a] Reaction conditions: 0.1 g/mL hydrochloride of (*R*)-**1a** with 98.5%ee; Solvent: ethyl benzoate. [b] performed on a column of Chiralpak OD-3. [c](*R*)-**1b** hydrochloride (98.0%ee) was the substrate; Measured on a column of Chiralpak IA; Heating in oil bath.

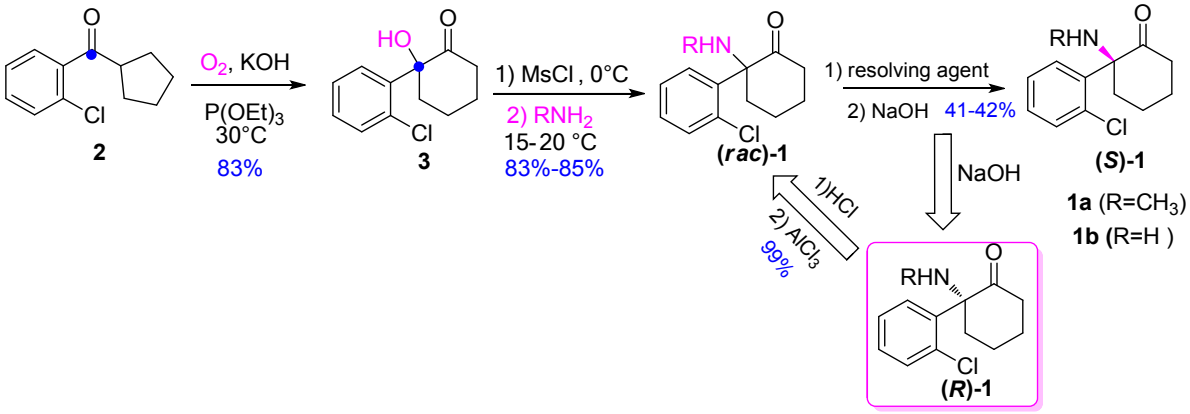
Scheme 7 the Recycling Procedure of (*R*)-1



When the reaction completed, the racemized ketamine or norketamine hydrochloride could obtained after a simple filtration from ethyl benzoate. The chemical purities of the racemized ketamine and norketamine were above 99.0%. Subsequently, the obtained hydrochloride was treated with 2 N NaOH aqueous

solution and the precipitated free base of ketamine or norketamine was subjected to a new resolution to get (*S*)-**1** in 41%-42% yield with >99.0% ee (**Scheme 7**). The yield of the resolution step was up to 80%, and the overall yield of this route could reach to 67.4% (28.9% without racemization) after two times recovery of the (*R*)-ketamine. This racemization process was concise and economical and could be applied to the industry to recycle the unwanted (*R*)-**1**, and (*S*)-**1** was obtained in high chiral purity via the resolution procedure.

Scheme 8. Our Concise Process of (*S*)-1



CONCLUSION

In conclusion, a concise and novel procedure was developed for the preparation of (*S*)-ketamine and (*S*)-norketamine via classic resolution followed by the racemization of the undesired isomer (**Scheme 8**). Starting from the commercially available substrate **2**, racemic ketamine was obtained through hydroxylation-rearrangement-amination in

two simple steps with >99.0% chemical purity. This procedure for the preparation of racemic ketamine and norketamine has obvious advantages including less production steps, mild reaction conditions, excellent quality and low production cost. The racemic ketamine and norketamine was separated by *L*-tartaric acid or *L*- pyroglutamic acid to give (*S*)-**1** isomer in the yield 41%-42% with 99.5% ee. This practicable process to racemize the undesired (*R*)-**1** hydrochloride was conducted in the ethyl benzoate under 150°C in the presence of 0.2 equiv $AlCl_3$, and the racemized ketamine and norketamine were obtained in quantitative yield with the chemical purity of 99.0%. The overall yield of this new route was increased to 67.4% from 28.9% with two times recycling of undesired isomer. This concise, efficient and economical procedure to (*S*)-ketamine and (*S*)-norketamine has distinct value in the industrial production.

EXPERIMENTAL SECTION

General. (2-chlorophenyl) (cyclopentyl) methanone **2** was prepared from our laboratory with the purity of 98.5%. Other chemicals were purchased from market and used as received. For the reactions that require heating, the heat source was oil bath. The 1D NMR and 2D NMR spectra were obtained on the Avance III 600 MHz and 400 MHz spectrometers (Bruker, Karlsruhe, Germany). The samples were dissolved with $CDCl_3$, DMSO-d_6 and MeOD. HRMS spectral data were recorded using a Bruker maxis 4G-TOF mass spectrometer. The DSC spectra were performed on the TA Instruments DSC Q2000 apparatus.

The optical rotations values were determined by an Anton Paar MCP 500 polarimeter at 20°C, 589nm (sodium ray). The TGA spectra were obtained from a TA TGA Q500 analyzer. The data of SCXRD were acquired on a Bruker D8 VENTURE. Chemical purity was determined with a Dionex UltiMate 3000 chromatograph system using a DAD detector. The mobile phase was ACN (A) and 10 mM KH_2PO_4 aqueous solution (B); Column: Waters X-Bridge (C18, 4.6 mm × 150 mm, 3.5 μm); Column temperature: 35°C, Wavelength: 210nm. LCMS spectra was obtained on an Agilent LC/MS system including an Agilent 1260-LC system, a single quadruple mass detector (Agilent Technologies, Santa Clara, CA, USA). The optical purity was recorded on a Dionex UltiMate 3000 chromatograph system with a Chiralpak OD-3 column (4.6 mm × 250 mm, 3.0 μm) for (*S*)-ketamine at a flow rate of 0.8 mL/min; the mobile phase was n-hexane / 2-propanol (95:5); Wavelength: 210 nm. For (*S*)-norketamine: Chiralpak IA column (4.6 mm × 250 mm, 5.0 μm); the eluent and wavelength were same as (*S*)-ketamine.

Synthesis of 2-(2-chlorophenyl)-2-hydroxycyclohexanone (3). The (2-chlorophenyl) (cyclopentyl) methanone **2** (50.0 g, 0.24 mol), $P(OEt)_3$ (59.8 g, 0.36 mol), ethanol (500 mL), and KOH (13.5g, 0.24mol) were added to a 1.0 L three-necked flask under an atmosphere of oxygen in a balloon. The mixture was stirred under 30°C for 48h. When the HPLC showed that **2** was less than 0.5%, the reaction was regarded as completed. In workup procedure, the mixture was decompressed to remove most ethanol (about 330 mL).

Subsequently, the obtained suspension was diluted slowly with 1500 mL deionized water, meanwhile, stirred vigorously for 2h at 5-10 °C. The diluted suspension was filtered to isolate the precipitates which was then washed three times with deionized water (500 ml) followed by vacuum drying at 50°C to obtain the faint yellow solid **3** (44.8 g, yield 83.4%, HPLC purity 99.1%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.42 – 7.33 (m, 2H), 7.32 – 7.25 (m, 1H), 4.51 (s, 1H), 3.04 – 2.88 (m, 1H), 2.68 – 2.54 (m, 1H), 2.46 (td, *J* = 11.9, 5.8 Hz, 1H), 2.07 (dd, *J* = 12.7, 4.0 Hz, 1H), 1.85 – 1.71 (m, 4H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 212.6, 137.5, 133.9, 131.3, 129.7, 128.6, 127.1, 80.6, 41.8, 38.8, 29.5, 22.8. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{12}H_{13}O_2NaCl$: 247.0502; Found 247.0509. The assignment is supported by an X-ray crystallographic structure determination.

Synthesis of 2-(2-chlorophenyl)-2-(methylamino) cyclohexanone (ketamine, 1a). A 250 mL reactor was charged with **3** (20.0 g, 0.089 mol), triethylamine (31.6 g, 0.312 mol), and tetrahydrofuran 130 mL in nitrogen atmosphere. Mesyl chloride (30.6 g, 0.267 mol) combined with 30 mL tetrahydrofuran was added to the mixing system drop by drop. The temperature was maintained at -5-0 °C through regulating the dropping speed. After finishing the dropping, the mixture was stirred for another 1h. It was regarded proceed to the next operation when the HPLC showed that **3** was below to 1.0%. 30% methylamine ethanol solution (120 mL) were put in the reactor, subsequently, the temperature was gradually rised to 15-20 °C and continued stirring 3-4h. In workup procedure, most of the

EtOH and THF were evaporated at negative pressure followed by 150 mL water and dichloromethane were added. After the extraction, aqueous phase was discarded, and organic phase was acidated with 1N dilute hydrochloric acid to the pH at 3-4. Then, the collected upper aqueous phase was alkalized to the pH = 9-10 by using 1N sodium hydroxide. Subsequently, the alkalized water phase was extracted by dichloromethane (150 mL) three times and then dichloromethane was dried with anhydrous Na_2SO_4 followed by desolventizing to yield the ketamine. The obtained solid underwent vacuum drying process at 50 °C to get the crude ketamine (18.0 g, yield: 85.3%, HPLC purity 99.5%). 1H NMR (400 MHz, MeOD) δ 7.99 (dd, J = 6.1, 2.4 Hz, 1H), 7.70 – 7.62 (m, 3H), 4.87 (s, 2H), 3.52 – 3.38 (m, 1H), 2.63 – 2.52 (m, 2H), 2.43 (s, 3H), 2.21 – 2.13 (m, 1H), 2.02 – 1.91 (m, 2H), 1.80 (qdd, J = 12.9, 9.2, 4.2 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, MeOD) δ 206.5, 134.0, 132.1, 131.5, 131.5, 128.0, 127.4, 71.9, 39.0, 35.8, 29.2, 26.3, 21.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{17}ClNO$: 238.0999; Found 238.0996.

Synthesis of 2-amino-2-(2-chlorophenyl) cyclohexanone hydrochloride (1b). A 250 mL reactor was charged with **3** (20.0g, 0.089mol), triethylamine (31.6g, 0.312mol), and tetrahydrofuran 130 mL in nitrogen atmosphere. Mesyl chloride (30.6 g, 0.267 mol) combined with 30 mL tetrahydrofuran was dropped to the mixing system. The temperature was kept at -5-0 °C through controlling the dropping rate. After finishing the dropping, the mixture was stirred for another 1h. It was regarded proceed to the next operation when the HPLC showed that **3** was below to 1.0%. Added 7.0 mol/L ammonia

methanol solution (130 mL) to the reaction mixture, subsequently, the temperature was gradually rised to 15-20°C. The workup procedure was the same as ketamine. The obtained solid was underwent vacuum drying process at 50 °C to get the crude norketamine (16.5 g, yield: 83.0%, HPLC purity 97.2%). ^{1}H NMR (600 MHz, DMSO) δ 8.82 (s, 3H), 7.90 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.61 – 7.52 (m, 3H), 3.18 (dd, *J* = 14.3, 2.7 Hz, 1H), 2.48 (dd, *J* = 9.1, 6.2 Hz, 1H), 2.40 (td, *J* = 12.5, 5.9 Hz, 1H), 2.03 (dd, *J* = 7.6, 4.5 Hz, 1H), 1.96 (td, *J* = 14.2, 3.5 Hz, 1H), 1.79 (d, *J* = 13.9 Hz, 1H), 1.70 – 1.51 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, DMSO) δ 207.5, 133.7, 132.3, 132.0, 131.8, 131.6, 128.6, 67.2, 39.3, 38.1, 29.6, 21.5. HRMS (ESI-TOF) m/z: [M+H] $^{+}$ Calcd for $C_{12}H_{15}ClNO$: 224.0842; Found 224.0848.

Synthesis of (*S*)-2-(2-chlorophenyl)-2-(methylamino) cyclohexanone tartrate (Esketamine tartrate). A 250 mL reactor was charged with ketamine base (18.0 g, 0.058mol), *L*-tartaric acid (4.8g, 0.032mol) and the solvent of acetone (168mL) and water (12mL). The reaction mixture was heated to reflux for 30 min until it was clarified and then cooled naturally to 55-58°C. Add a few crystal seeds to the clear solution, and keep stirring at 55°C for 2h, after that, cool the suspension to 10-15°C at the rate of about 5 °C/h. After stirring overnight, the precipitates were obtained through simple filtration and washed two times with acetone (300mL). The (*R*)-**1a** was collected from mother liquor through decompression concentration for the next resolution. The crude product underwent vacuum drying process overnight and yield the esketamine tartrate

13.3g (>99.5% ee, chemical purity >99.5%, yield: 41.5%), [α]20 D +65.8 (*c* 1.0, H_2O). (lit., [20a] [α]20 D +68.8 (*c* 2.0, H_2O)).

Synthesis of (*S*)-2-(2-chlorophenyl)-2-(methylamino) cyclohexanone hydro chloride, (*S*)-1a. The obtained tartrate (13.0g, 0.03mol) was alkalized with 1N NaOH aqueous solution (50mL). Subsequently, the suspension was filtered to isolate the precipitates which were then washed two times with 50 ml H_2O followed by the vacuum drying process to obtain the esketamine base (7.2 g). After salting with 2.0 N HCl-EA, the esketamine hydrochloride was obtained and went through the vacuum dry to constant weight at 40°C (8.2 g). A 250mL three necked flask was charged with crude esketamine hydrochloride, deionized water (9mL) and acetone (75mL) which was heated at 65°C for 1h. When the clear solution cooling to 50 °C, a small amount of crystal seeds were added and then kept stirring at 50 °C for 2h. Subsequently, cool the suspension to room temperature at the rate of about 5 °C/h. Subsequently, the suspension was filtered to isolate the precipitates and then washed with 50 mL acetone two times followed by vacuum drying to give esketamine hydrochloride. (6.56g, yield: 80.2%, 99.9% ee, and chemical purity >99.8%). [α]20 D +91.522 (*c* 1.0, H_2O). ^{1}H 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{^{1}H} NMR (101 MHz, MeOD) δ 206.5, 134.0, 132.1, 131.5, 131.5, 128.0, 127.4, 71.9, 39.0, 35.8, 29.2, 26.3, 21.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{17}ClNO$:

238.0999; Found 238.1002. 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. The assignment is supported by an X-ray crystallographic structure determination.

Synthesis of (*S*)-2-amino-2-(2-chlorophenyl)cyclohexanone hydrochloride, (*S*)-1b. Similarly, The resolution of norketamine by using *L*- pyroglutamic acid in EtOH / H_2O at the ratio of 12:1. Racemic norketamine base (16.0g, 0.0717 mol) and 100 mL ethanol were added to 250 mL reactor. The mixture was heated in the oil bath at 65°C for 30 min until the solution was clarified. *L*-pyroglutamic acid (5.1 g, 0.0394 mol) was dissolved in the mixture of 48mL ethanol and 12mL deionized water to be a clarified solution, and then dropped to the mixture. The clear solution was kept stirring at 75°C for 1h. Subsequently, cool the suspension to 15°C at the rate of about 5 °C/h. Subsequently, the precipitates were isolated via vacuum filtration and then washed with 100 mL ethanol three times followed by vacuum drying to give crude product 10.6 g (99.4% ee, yield: 42%). Anal. Calcd for $C_{12}H_{14}ClNO$: C, 64.43; H, 6.31; N, 6.26. Found: C, 64.36; H, 6.29; N, 6.27. [α]20 D -72.038 (*c* 1.0, MeOH).

According to the operation procedure of (*S*)-ketamine hydrochloride, the (*S*)-norketamine hydrochloride was obtained. (7.9g, yield: 79.6%, 99.6% ee, chemical purity >99.8%).^{1}H NMR (400 MHz, DMSO) δ 8.84 (s, 3H), 7.89 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.62 – 7.49 (m, 3H), 3.18 (dd, *J* = 14.3, 2.5 Hz, 1H), 2.48 – 2.34 (m, 2H), 2.05 – 1.88 (m, 2H), 1.85 – 1.73 (m, 1H), 1.70 – 1.50 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 206.9, 133.2, 131.8, 131.5, 131.3, 131.1,

128.1, 66.7, 37.6, 29.1, 21.1. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{15}ClNO$: 224.0842; Found 224.0846.

The Racemization of (*R*)-1 isomer. The (*R*)-**1** was collected from mother liquors through decompression concentration and then the obtained solid was alkalized with 1 N NaOH. Subsequently, the (*R*)-**1** base was underwent vacuum drying process at 50 °C to constant weight and then salted with EA-HCl to yield the (*R*)-**1** hydrochloride. The (*R*)-**1a** hydrochloride (9.0g, 0.038mol) was dissolved in 90 mL ethyl benzoate and stirred in the presence of $AlCl_3$ (1.0 g, 0.0076 mol) at the temperature of 150 °C by heating in oil bath. After the (*R*)-**1a** was racemized completely, the suspension was cooled naturally to 10-15°C. In order to precipitate the product fully, 50mL cyclohexane was added to the mixture. The precipitates were filtered, washed, and dried to give the racemized **1** ((*R*)-**1a**/(*S*)-**1a**) (50.3%/49.7%) 9.3 g. The yield of this racemization was quantitative and the chemical purity of the product was 99.5%. The racemization process of (*R*)-**1b** hydrochloride is the same as that of (*R*)-**1a.**

ASSOCIATED CONTENT

Supporting Information

Analytical spectrograms of **3**, Ketamine, Norketamine, (*S*)-norketamine and (*S*)-ketamine; SCXRD of **(*S*)-ketamine hydrochloride** and compound **3**; The Analytical spectra of the **racemized Ketamine and Norketamine**;

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