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REGULAR ARTICLE

Synthesis of ketamine from a nontoxic procedure: a new and efficient route

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Abstract. Ketamine [2-(2-chlorophenyl)-2-methylamino-cyclohexan-1-one] has been used in both veterinary and human medicine. In this research, a new and efficient protocol has been developed for the synthesis of ketamine, by using hydroxy ketone intermediate. Synthesis of this drug has been done in five steps. At first, the cyclohexanone was made to react with 2-chlorophenyl magnesium bromide reagent followed by dehydration in the presence of an acidic ionic liquid, 1-methyl-3-[2-(dimethyl-4-sulfobutyl-ammonium) ethane] imidazolium hydrogen sulfate to obtain 1-(2-chlorophenyl)-cyclohexene. The oxidation of the synthesized alkene by potassium permanganate gave corresponding hydroxy ketone intermediate. The imination of this intermediate by methyl amine and finally the rearrangement of the obtained imine at elevated temperature resulted in the synthesis of ketamine. All of the intermediates and the product were characterized by ^{1}H-NMR and IR spectroscopies. No need to use toxic bromine (which is used in most of the reported procedures for the synthesis of ketamine), high reaction yields and use of commercially available and safe materials and no need to use corrosive acids in the dehydration step are some of the advantages of this procedure over the common reported ones for the snthesis of ketamine.

Keywords. Ketamine; anesthetic drug; acidic ionic liquid; nontoxic procedure; 2-hydroxycyclohexanone.

1. Introduction

Ketamine (Figure 1) is an anesthetic and analgesic drug used in both human[1–3] and veterinary[4,5] medicines. It has also been used as antidepressant[6] and in treating alcohol addiction[7,8] and reflex sympathetic dystrophy.[9,10] In 1970, it was used as a battlefield anesthetic.[11]

Many efforts have been made to synthesis this compound and its derivatives, due to its importance and aforementioned applications.[12–17] In a most commonly used method (Stevens 1966), 2-chlorobenzonitrile reacts with cyclopentyl magnesium bromide reagent to synthesize ketone intermediate.[18] Further, this intermediate was brominated with bromine, imination of the carbonyl functional group, followed by thermal rearrangement produced ketamine (Scheme 1). The Stevens method is based on the formation and thermal rearrangement of the imine intermediate. This imine is synthesized from the bromination of 2-chlorophenyl cyclopentyl ketone with toxic bromine and then reaction with methylamine. Some of the drawbacks of these methods were use of toxic bromine, difficulty in thermal rearrangement step at a very high temperature with a low product yield.

Further in 2012, the ketamine was synthesized using 1,2-cyclohexanedione as the starting material.[19] In this method, first, one of the carbonyl groups of this compound was protected selectively to produce monoacetal compound. Then, the monoacetal reacted with Grignard reagent to produce the corresponding alcohol. In the second step, imination with methylamine was done and finally, thermal rearrangement of this imine produced ketamine and a five-membered ring as byproduct (Scheme 2). Use of expensive 1,2-cyclohexanedione as the starting material, low yield of the selective protection of one of the functional groups

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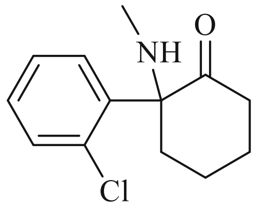
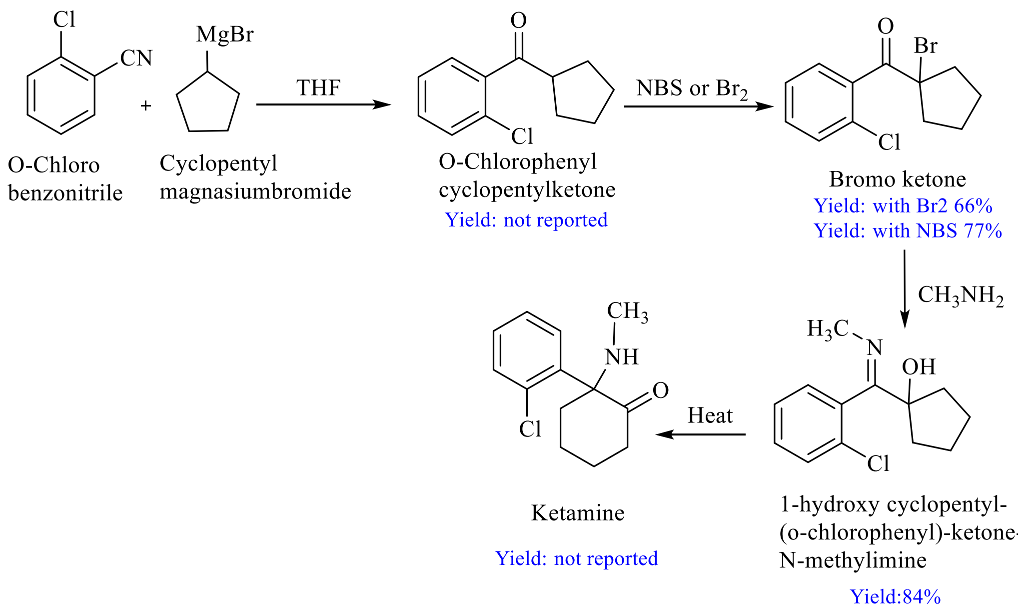


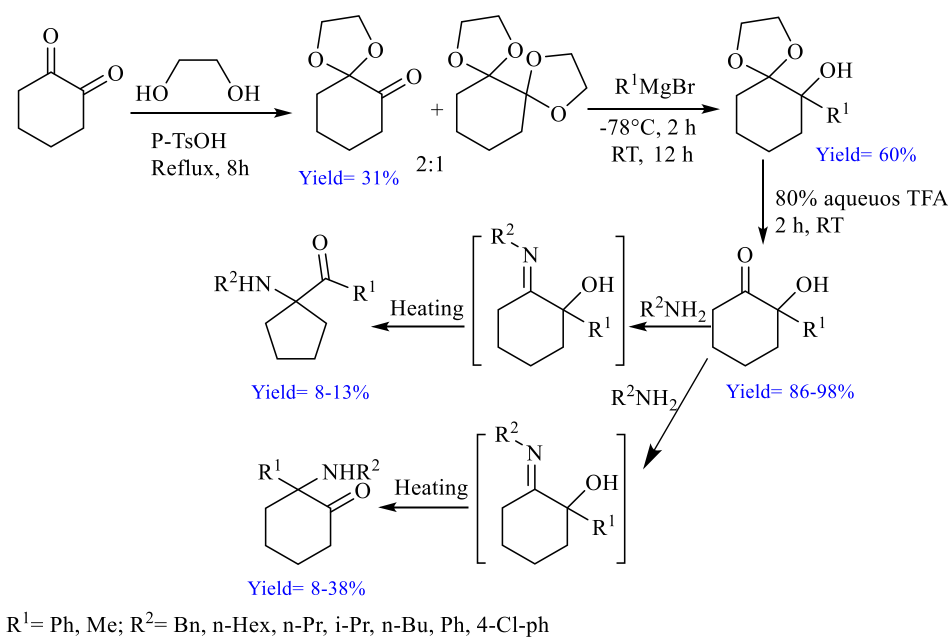
Figure 1. The structure of ketamine.

of the diketone, tedious separation of the protected monoacetal from diacetal compound and low yield of the rearrangement step are the disadvantages of this method.

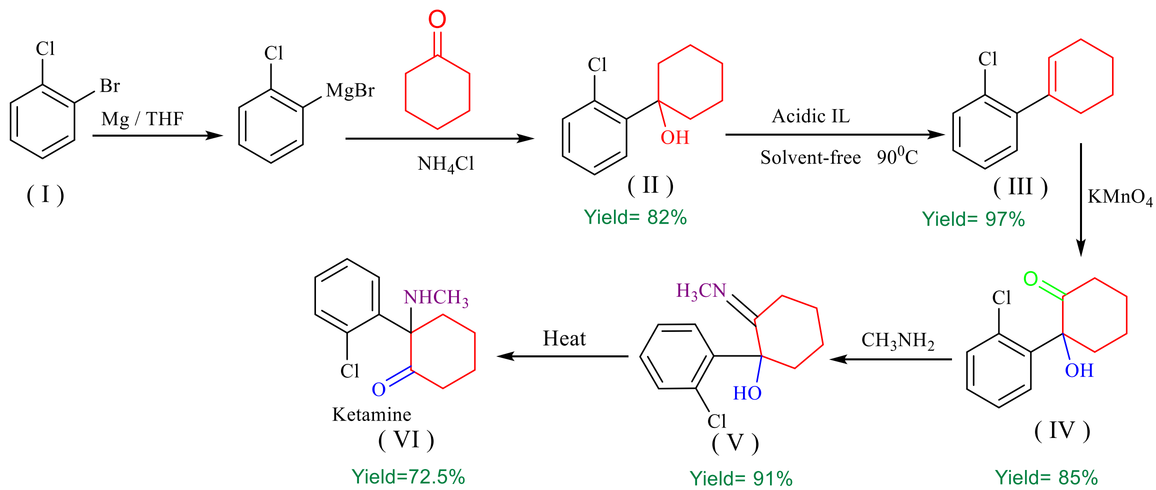
Due to the various applications of the ketamine and to rectify some drawbacks of the previous procedures such as low intermediates and low product yields, use of toxic bromine, complex process, selective protec-



Scheme 1. Synthetic route of ketamine from 2-chlorobenzonitrile[18].



Scheme 2. Synthetic route of ketamine from 1,2-cyclohexanedione[19].



Scheme 3. Synthetic route of ketamine from 1-bromo-2-chlorobenzene (designed in this study).

tion of one of the same carbonyl groups concomitant with low yield, we presented a new and efficient route for the synthesis of ketamine. The main objective of this study was to introduce a new method for the synthesis of ketamine, in which besides the high product yield, no toxic material should be used and more importantly being able to be scaled up. As task specific ionic liquids have many applications in organic syntheses[20,21] and as we have synthesized and applied different acidic ionic liquids for the green synthetic applications,[22–24] one of the other important aims of this project was to use these reagents instead of corrosive inorganic acids and toxic solvents. The designed steps for the ketamine synthesis is shown in Scheme 3.

2. Experimental

2.1 *Chemicals and apparatus*

All chemicals were purchased from Merck and Aldrich chemical companies. IR spectra were recorded on a Nicolet 800 instrument using KBr pellets or liquid film. ^{1}H-NMR and ^{13}C-NMR spectra were measured on a Bruker Avance DRX-500 MHz spectrometer in $CDCl_3$ and tetramethylsilane (TMS) as the internal standard. Elemental analysis (C, H, N) was performed using a Heraeus CHN rapid analyzer.

2.2 *Synthesis of 1-(2-chlorophenyl)-cyclohexane-1-ol (II)*

Five crystals of iodine were added to a mixture of magnesium (3.65 g, 150 mmol) in 500 mL dry tetrahydrofuran (THF). The mixture was refluxed for 2 h under N_2 atmosphere and was cooled to room temperature. The solution of 1-bromo-2-chlorobenzene (23.90 g, 125 mmol) in 250 mL dry THF was added dropwise to the mixture. The reaction mixture was stirred again at room temperature for 2 h under N_2 atmosphere. Subsequently, a solution of cyclohexanone (9.80 g, 100 mmol) in 500 mL THF was added dropwise to the reaction mixture. The mixture was stirred at room temperature for 24 h under N_2. Then, it was poured to a mixture of crashed ice and ammonium chloride. The organic layer was separated and washed with water and brine. It was dried over anhydrous $MgSO_4$. The solvent was evaporated by a rotary evaporator to generate 1-(2-chlorophenyl)-cyclohexan-1-ol as a crude product. Purifying the product by a silica gel column chromatography (20:3 hexane/ethyl acetate) produce pure alcohol as oily yellow liquid with 82% yield.

FT-IR (Neat): υ (cm^{-1}): 3742 (OH), 752 (C–Cl). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ (ppm):1.60–1.93 (8H, m, CH_2), 2.19–2.25 (2H, m, CH_2), 2.06 (1H, s, OH), 7.17–7.37 (3H, m, Ar-H), 7.66 (1H, d, Ar-H, $J = 7.0$ Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz): δ (ppm): 22.1, 26.0, 38.0, 72.9, 126.4, 128.1, 128.5, 129.2, 133.3, 135.6. Anal. Calcd. for $C_{12}H_{15}OCl$ C, 68.41; H, 7.12%. Found C, 68.40; H, 7.14%.

2.3 *Preparation of 1-methyl-3-[2-(dimethyl-4-sulfobutyl-ammonium) ethane] imidazolium hydrogen sulfate*

The acidic ionic liquid was synthesized according to our pervious reported work.[21]

2.4 *Synthesis of 1-(2-chlorophenyl)-cyclohexene (III)*

2.4a *Synthesis of 1-(2-chlorophenyl)-cyclohexene (III) in the presence of p-toluenesulfonic acid (PTSA)*: The synthesized alcohol **(II)** (21.05 g, 100 mmol), p-toluenesulfonic acid (2.10 g, 11 mmol) and 500 mL toluene were added to a three-neck flask equipped with a reflux condenser and the Dean–Stark apparatus. The reaction mixture was stirred at 110°C for 10 h under N_2 atmosphere. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, toluene was removed by rotary evaporator under reduced pressure. Further, 1.5 L dichloromethane and 500 mL $NaHCO_3$ (10%) were added. The organic layer was separated and dried over anhydrous $MgSO_4$. Finally, by evaporating the solvent and purifying with silica gel column chromatography (hexane), 1-(2-chlorophenyl)-cyclohexene was obtained as a pure colorless liquid (88% yield).

2.4b *Synthesis of 1-(2-chlorophenyl)-cyclohexene (III) in the presence of 1-methyl-3-[2-(dimethyl-4-sulfobutyl-ammonium) ethane] imidazolium hydrogen sulfate*: The synthesized alcohol **(II)** (21.05 g, 100 mmol) and 1-methyl-3-[2-(dimethyl-4-sulfobutyl-ammonium) ethane] imidazolium hydrogen sulfate (0.80 g, 2.0 mmol) were charged to a three-neck flask equipped with a reflux condenser and a Dean-Stark apparatus. Further, it was heated upto 90°C and maintained at the same temperature for 30 min. The progress of the reaction was monitored by TLC. The product (1-(2-chlorophenyl)-cyclohexene) was separated simply by extraction with hexane (2 × 25 mL) and dried over anhydrous $MgSO_4$. Finally, by evaporation of the solvent and purifying with a silica gel column chromatography, (hexane), 1-(2-chlorophenyl)-cyclohexene was obtained as a pure colorless liquid (97% yield).

FT-IR (Neat): υ (cm^{-1}): 1703 (C=C), 754 (C–Cl). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ (ppm): 1.68–1.73 (2H, m, CH_2), 1.76–1.79 (2H, m, CH_2), 2.19–2.22 (2H, td, CH_2, *J* = 9.0, 3.0 Hz), 2.30–2.33 (2H, m, CH_2), 5.68 (1H, t, –C=CH, *J* = 3.0 Hz), 7.16–7.27 (3H, m, Ar-H), 7.35 (1H, d, Ar-H, *J* = 7.5 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz): δ (ppm): 23.0, 23.4, 26.2, 30.0, 117.9, 127.0, 128.9, 130.0, 130.8, 132.0, 132.8, 133.1. Anal. Calcd. for $C_{12}H_{13}Cl$ C, 74.80; H, 6.75%. Found C, 74.80; H, 6.74%.

2.5 *Synthesis of 2-(2-chlorophenyl)-2-hydroxycyclohexane-1-one (IV)*

The 1-(2-chlorophenyl)-cyclohexene (14.40 g, 75 mmol) was added to a mixture of 150 mL H_2O and 370 mL acetone. Further, acetic acid (12.5 mL) was added to the reaction mixture and stirred for 45 min at room temperature. Then $KMnO_4$ (16.60 g, 105 mmol) dissolved in 37.5 mL of H_2O and 150 mL of acetone was added dropwise to the reaction mixture. The mixture was stirred for 1 h at room temperature. The progress of the reaction was monitored by TLC. Subsequently, a solution of sulfuric acid:H_2O (75:600) was slowly added and stirred for 30 min at room temperature. $NaNO_3$ (10.20 g, 120 mmol) was then added and stirred for 30 min at room temperature, and 800 mL of diethyl ether was added. The organic layer was neutralized with NaOH. After separation of the organic layer, it was dried with $MgSO_4$. Finally, evaporation of the solvent via rotary evaporator and purifying the product via silica gel column chromatography (20:3 hexane/ethyl acetate) produced 2-(2-chlorophenyl)-2-hydroxy cyclohexan-1-one as yellow liquid (yield, 85%).

FT-IR (Neat): υ (cm^{-1}): 3446(OH), 1722 (C=O), 1269 (C–O), 756 (C–Cl). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ (ppm): 1.53–1.68 (2H, m, CH_2), 1.87–1.96 (2H, m, CH_2), 2.41 (2H, tt, Ph-C(OH)-C$\underline{H_2}$-, *J* = 6.0, 2.0 Hz), 2.58 (2H, tt, O=C–C$\underline{H_2}$–, *J* = 7.5,2.5 Hz), 6.42 (1H, s, OH), 7.28–7.40 (3H, m, Ar-H), 7.59 (1H, d, Ar-H, *J* = 8.0 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz): δ (ppm): 18.0, 26.6, 30.1, 35.1, 92.8, 126.2, 128.1, 129.8, 130.1, 133.7, 137.4, 204.0. Anal. Calcd. for $C_{12}H_{13}ClO_2$ C, 64.14; H, 5.79%. Found C, 64.17; H, 5.78%.

2.6 *Synthesis of 2-hydroxy-2-(2-chlorophenyl)-1-cyclohexane-N-methylimine (**V**)*

In a 250 mL round bottom flask, 2-(2-chlorophenyl)-2-hydroxycyclohexane-1-one (11.20 g, 50 mmol), K_2CO_3 (2.05 g, 15 mmol) and 50 mL methylamine were poured, and kept in dark and stirred for 48 h at room temperature. Further, the reaction mixture was washed with dry THF, filtered and the solvent was evaporated by rotary evaporator. Finally, purification of the product by a silica gel column chromatography (20:3 hexane/ethyl acetate) produced 2-hydroxy-2-(2-chlorophenyl)-1-cyclohexane-*N*-methylimine as a white liquid (yield 91%).

FT-IR (Neat): υ (cm^{-1}): 3744 (OH), 1645 (C=N), 1262 (C–O), 756 (C–Cl). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ (ppm): 0.59 (3H, s, CH_3), 1.59–1.65 (2H, m, CH_2), 1.76–1.83 (2H, m, CH_2), 2.68 (2H, tt, Ph-C(OH)-C$\underline{H_2}$-, *J* = 7.5, 2.5 Hz) 2.83 (2H, tt, –N = C–C$\underline{H_2}$–, *J* = 6.0, 2.0 Hz), 6.62 (1H, s, OH), 7.46–7.59 (3H, m, Ar-H), 7.79 (1H, d, Ar-H, *J* = 7.5 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz): δ (ppm): 18.0, 26.9, 27.1, 29.4, 43.0, 72.8, 127.1, 128.4, 129.8, 130.0, 135.5, 137.2, 163.9. Anal. Calcd. for $C_{13}H_{16}NClO$ C, 65.68; H, 6.74; N, 5.89%. Found C, 65.68; H, 6.73; N, 5.90%.

2.7 *Synthesis of ketamine (**VI**)*

In a round bottom flask, 2-hydroxy-2-(2-chlorophenyl)-1-cyclohexane-*N*-methylimine (5.90 g, 25 mmol) was added to 120 mL of decaline. The mixture was stirred at 170°C for 4 h. The organic product was extracted with HCl (0.1 M). Then the reaction mixture was neutralized with NaOH (0.1 M). The product was extracted with dichloromethane. After evaporation of the solvent, ketamine was obtained as a colorless oil (yield, 72.5%).

FT-IR (Neat): υ (cm^{-1}): 3421 (N–H), 1748 (C=O), 756 (C–Cl). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ (ppm):1.67–1.74 (2H, m, CH_2), 1.77–1.85 (2H, m, CH_2), 2.76 (2H, tt, C(NH)-C$\underline{H_2}$, *J* = 7.5, 2.5 Hz), 2.79 (1H, s, NH), 2.82 (2H, tt, O=C–C$\underline{H_2}$–, *J* = 6.0, 2.0 Hz), 3.78 (3H, s, CH_3), 7.65–7.74 (3H, m, Ar-H), 7.79 (1H, d, Ar-H, J = 8.0 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz): δ (ppm): 19.1, 28.5, 31.6, 34.9, 36.9, 82.0, 127.9, 128.2, 128.8, 130.5, 133.1, 137.3, 208.3. Anal. Calcd. for $C_{13}H_{16}NClO$ C, 65.68; H, 6.74; N, 5.89%. Found C, 65.69; H, 6.74; N, 5.91%.

3. Results and Discussion

As it has been shown in Scheme 3, the reaction between 2-chlorophenylmagnesium bromide and cyclohexanone, there after dehydration with acidic IL and oxidation with $KMnO_4$ resulted in the synthesis of the intermediate (**IV**). Finally, the reaction of methylamine with this intermediate and thermal rearrangement of the produced imine (**V**) produced ketamine. To increase the yield of the synthesis of the alcohol (**II**), some optimizations were done. Effect of some parameters such as molar ratio of the reactants and the reaction temperature on the synthesis of alcohol (**II**) were investigated. The result of these optimizations is shown in Table 1.

Table 1. Optimization of the reaction conditions of the synthesis of the alcohol (**II**)[a].

Entry	1-Bromo-2-chlorobenzene (mmol) (**I**)	Temperature (°C)	Yield (%)[b]
1	1	0	Trace
2	1	10	Trace
3	1	25	74
4	1	66	70
5	1.10	25	78
6	1.25	25	82
7	1.40	25	82

[a]1 mmol of cyclohexanone was used in all experiments.
[b]Yield was determined relative to the cyclohexanone amount.

As can be seen, the best result was obtained by choosing 1.25 molar ratio of 1-bromo-2-chlorobenzene to the cyclohexanone and setting the temperature at 25°C.

The considerable point, in other words, the innovation of this study was the selection of the dehydration followed by oxidation of the alkene (**III**) to ketol (**IV**); which makes it possible to design a new method to achieve the ketamine. Dehydration of the alcohol (**II**) was tested in two different condition, use of PTSA in toluene as solvent and use of acidic IL as reagent and solvent. The results are shown in Table 2.

Table 2 shows that a best result was obtained in the presence of acidic IL. The advantages of using acidic IL for the dehydration step is that not necessary to use the corrosive acids and toxic solvents, in addition to high dehydration yield and also reusability of IL. The plausible mechanism for dehydration step is shown in Figure 2.

Oxidation of the synthesized alkene (**III**) with $KMnO_4$ produced 2-(2-chlorophenyl)-2-hydroxy cyclohexane-1-one (**IV**) as an important intermediate (Scheme 4).

In the fourth step, imination of (**IV**) was carried out by the reaction of this compound with methylamine. The reaction was carried out in the presence of 0.04 g of potassium carbonate and in the dark and solvent-free conditions (Scheme 5).

Finally, thermal rearrangement of (**V**) produced ketamine.

Table 2. Synthesis of alkene (**III**) from dehydration of alcohol (**II**) in the presence of PTSA or acidic IL.

Entry	Reagent/amount mol (%)	Solvent	Temperature (°C)	Time	Yield (%)[a]
1	PTSA/10	Toluene	110	10 h	88
2	Acidic IL/1	Solvent-free	90	30 min	97

[a]Isolated yields.

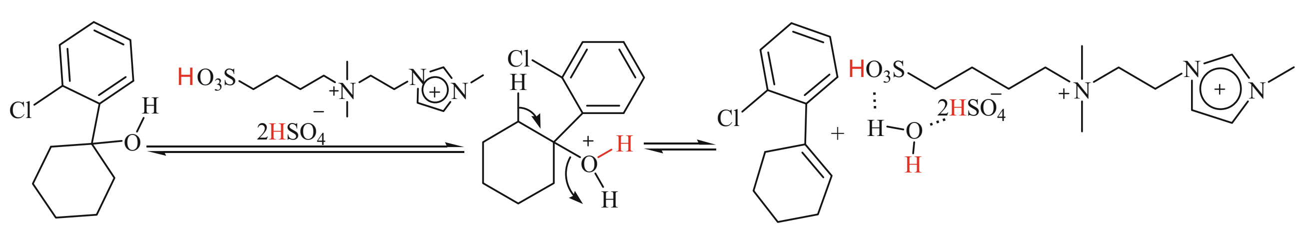
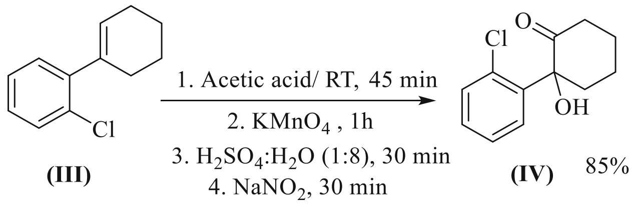
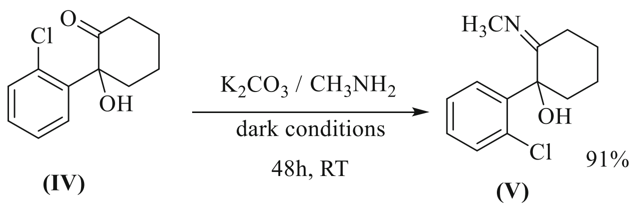


Figure 2. Dehydration of the 1-(2-chlorophenyl)-cyclohexane-1-ol(**II**) with acidic ionic liquid.



Scheme 4. Synthesis of 2-(2-chlorophenyl)-2-hydroxycyclohexane-1-one from 1-(2-chlorophenyl)-cyclohexene.



Scheme 5. Synthesis of 2-hydroxy-2-(2-chlorophenyl)-1-cyclohexane-*N*-methylimine from 2-(2-chlorophenyl)-2-hydroxycyclohexane-1-one.

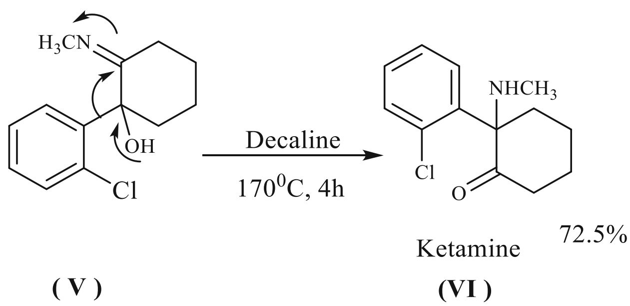


Figure 3. Plausible mechanism of the thermal rearrangement of 2-hydroxy-2-(2-chlorophenyl)-1-cyclohexane-*N*-methylamine (**V**) to ketamine.

This step was done in two different high boiling point solvents: decaline and diphenyl ether. The results showed that when the rearrangement was carried out in diphenyl ether, the yield of this step was 50%, but the use of dacaline as a solvent in this step improved the yield upto 72.5%, thus decaline was used as a solvent for the rearrangement step and the temperature was elevated to its reflux temperature (170°C) to obtain the best result. The thermal rearrangement step mechanism is shown in Figure 3.

4. Conclusions

In conclusion, in accordance to the importance of the synthesis of the ketamine and on the other hand, the draw backs of the reported procedures for the synthesis of this drug, a new and efficient route for the synthesis of ketamine has been developed. In this procedure, the ketamine was synthesized from 1-bromo-2-chlorobenzene in a safe five-step process. The conditions of each step were optimized. All the intermediates and the products were characterized by ^{1}H-NMR and IR spectroscopies. We focused in this study on the deletion of the toxic bromine, which is the main reagent of the most reported procedures for the synthesis of ketamine. Also, we used acidic IL as a safe, green and reusable reagent for the solvent-free dehydration step. Another important issue was the improvement of the yield; fortunately, we succeeded. High yields of the products, use of available and safe materials and deletion of toxic bromine from the procedure are the advantages of this method.

Supplementary Information (SI)

All additional information pertaining to characterization of the compounds using ^{1}H-NMR and IR spectra are provided in the supporting information available at www.ias.ac.in/chemsci.

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