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ORIGINAL PAPER

A novel strategy for the asymmetric synthesis of (*S*)-ketamine using (*S*)-*tert*-butanesulfinamide and 1,2-cyclohexanedione

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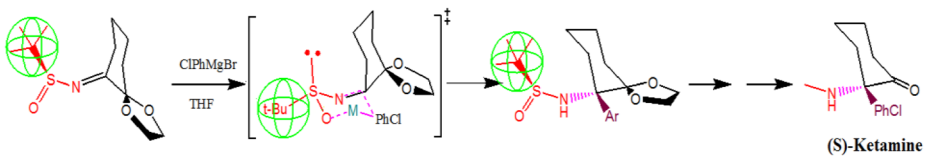
Abstract

We present a novel asymmetric synthesis route for synthesis of (*S*)-ketamine using a chiral reagent according to the strategy (Scheme 1), with good enantioselectivity (85% ee) and yield. In this procedure, the (*S*)-*tert*-butanesulfinamide (TBSA) acts as a chiral auxiliary reagent to generate (*S*)-ketamine. A series of new intermediates were synthesized and identified for the first time in this work (2–4). The monoketal intermediate (1) easily obtained after partial conversion of one ketone functional group of 1,2-cyclohexanedione into a ketal using ethylene glycol. The sulfinylimine (2) was obtained by condensation of (*S*)-*tert*-butanesulfinamide (TBSA) with (1), 4-dioxaspiro[4.5]decan-6-one in 90% yield. The (*S*)-*N*-*tert*-butanesulfinyl ketamine (3) was prepared on further reaction of sulfinylimine (2) with appropriate Grignard reagent (ArMgBr) in which generated chiral center in 85% yield and with 85% diastereoselectivity. Methylation of amine afforded the product (4). Finally, the sulfinyl- and ketal-protecting groups were removed from the compound (4) by brief treatment with stoichiometric quantities of HCl in a protic solvent gave the (*S*)-ketamine in near quantitative yield.

Graphical abstract



Keywords (*S*)-Ketamine · Asymmetric synthesis · (*S*)-*tert*-Butanesulfinamide · 1,2-Cyclohexanedione · Monoketal · Enantioselective construction

Introduction

Ketamine is used in medicine as an anesthetic; however, due to the hallucinations it may cause, it is not typically used as a primary anesthetic, in combination with other drugs [1–7]. Ketamine has been classified as an NMDA receptor antagonist but its mechanism was not well understood as of 2017 [8]. The *S*(+) and *R*(−) ketamine bind with different affinities: Ki = 3200 and 1100 nM, respectively [9–15]. There are some reports on the synthesis of α-phenyl cycloalkanones in the literature [16]. Such ketones have been the targets to some studies followed by Calvin L. Stevens et al. using aryl–alkyl migration, ring contraction, ring expansion and

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rearrangement of phenyl α-aminoketones [17–29]. Enantioselective construction of nitrogen-substituted quaternary carbon centers adjacent to the carbonyl group in the cyclohexane ring was performed with respect to the asymmetric synthesis of (*S*)-ketamine anesthetic. A few report for asymmetric synthesis of (*S*)-ketamine were recorded in the literature. Recently, Kiyooka et al. presented two procedures for this propose [30]. At first procedure, the phenyllithium was reacted to chiral α-ketoketal bearing chiral auxiliary on a ketone group with 83% yield and 82% de. However, the reaction of 2-chlorophenyllithium did not perform in which this procedure was unavailable for the (*S*)-ketamine. At second procedure, a different strategy was designed, which the chiral carbon of ketamine with a reduction step by *S*-BINAL catalyst was obtained (> 99% ee). Beside, Biermann et al. were presented a new method, the chirality induction prepared using Sharpless Dihydroxylation and followed with Ritter reaction. Finally, the obtained alcohol amine was converted to (*S*)-norketamine by Jones oxidation (= 99% ee) [31].

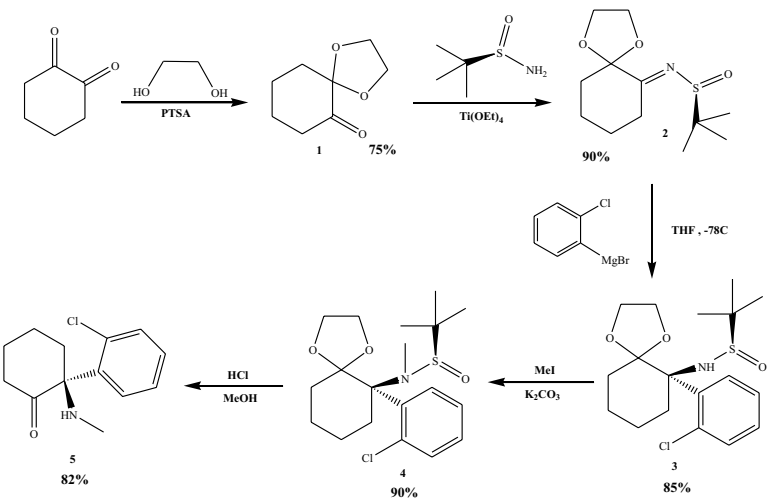
On the other hand, the synthesis of chiral amines is important to both academic and pharmaceutical research. During the past few years, one of main research lines has focused on the use of *N*-(*tert*-butylsulfinyl) imines in asymmetric synthesis [32–41]. We were willing to find a practical method for synthesis of this kind chiral imine in high yield and purity. Direct nucleophilic addition of the chiral *tert*-butanesulfinyl group to the imine and reduction deprotonation competition at the α-carbon. The *tert*-butanesulfinyl ketimines have been reacted with organometallic reagents with good yields and high diastereoselectivity to provide the tertiary carbinamines [42–47]. Because the general and efficient methods for the asymmetric synthesis of this class of amines are not accessible now [42–44, 48]. We report here on the preparation of quaternary carbon by the addition of Grignard reagent to *N*-sulfinyl imine derived from ketaled cyclohexanone. In this new procedure, the (*S*)-ketamine was prepared after nucleophilic addition of *N*-sulfinyl cyclic imine where both conditions of ring and the sulfinyl group have the potential to control of diastereoselectivity reaction. As far as we know, this is the first time that the three new intermediates (2–4) were synthesized and identified in the present study in which are differed from the previously reported compound (Scheme 1).

Results and discussion

Synthesis of the target (*S*)-ketamine started with the preparation of cyclic monoketal from the 1,2-cyclohexandione (Scheme 2) [30, 46, 49–51]. The monoketal **1** is obtained with moderate yield due to the high reactivity of monoketal and conversion to diketal.

Ketalization of 1,2-cyclohexanedione with ethylene glycol in a Dean–Stark device afforded a 1:3 mixture of diketal and monoketal after reflux. Although the azeotropic removal of H_2O should, in principle, shift the equilibrium towards the undesired diketal byproduct and the reaction could not

Scheme 1 Asymmetric synthesis of *S*-ketamine



Scheme 2 Preparation of monoketal

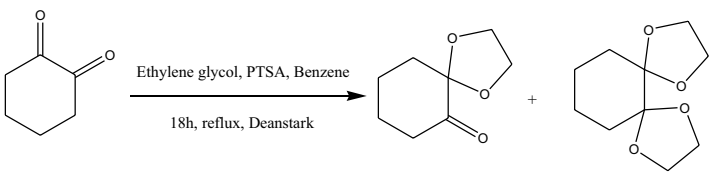
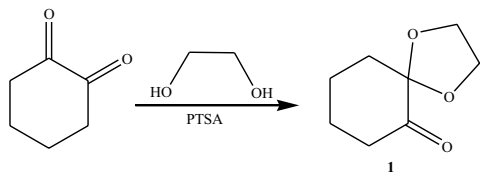


Table 1 Ketalization of 1,2-cyclohexandione with ethylene glycol and PTSA

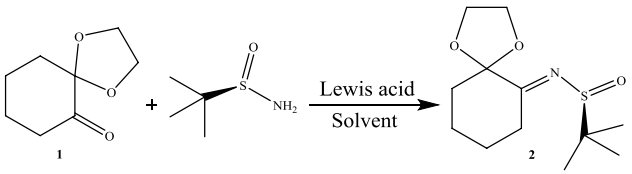


Entry	PTSA (%mol)	Solvent	Time (h)	Yield[a] (%)
1	0.2	Benzene	8	30
2	0.2	Benzene	18	75
3	0.4	Benzene	18	45
4	0.2	Benzene	24	50
5	0.2	Toluene	18	45
6	0.4	Toluene	18	30

The reaction could not be driven to completion and starting materials remain

[a]Yield determined by ^{1}H NMR analysis

Table 2 Condensations of TBSA with 1 mediated by Ti(IV) compounds



Entry	Lewis acid[a]	Solvent	Time (h)	Yield[b] (%)
1	$Ti(OEt)_4$	THF	3	80
2	$Ti(OEt)_4$	THF	6	90
3	$Ti(OEt)_4$	THF	12	75
4	$Ti(OEt)_4$	THF	24	70
5	$Ti(OEt)_4$	Toluene	6	79
6	$Ti(O\text{-}i\text{-}Pr)_4$	THF	3	73
7	$Ti(O\text{-}i\text{-}Pr)_4$	THF	6	80
8	$Ti(O\text{-}i\text{-}Pr)_4$	THF	12	65
9	$Ti(O\text{-}i\text{-}Pr)_4$	THF	24	62
10	$Ti(O\text{-}i\text{-}Pr)_4$	Toluene	6	65

[a]Mol ratio of Lewis acid to monoketal, 2–1

[b]Yield determined by NMR analysis

be driven to completion, probably because of the competing polymerization of ethylene glycol which delivered H_2O to the medium. After extensive experimentation, we found that the best reaction conditions involved performing *P*-toluenesulfonic acid (PTSA)-mediated ketalization in benzene after 18 h. (entry 2 Table 1). In the presence of PTSA catalyst, under acidic condition, the carbonyl group of 1,2-cyclohexandione is protonated, which activates it towards nucleophilic attack of ethylene glycol.

The reaction was performed in a Dean–Stark device and monoketal was separated by chromatography from the mixture and subjected to hydrolysis. In this way, the preparation of monoketal can be achieved in 75% yield. The key step in this approach is the hydrolysis of diketal, by acidic treatment (PTSA), in which afforded monoketal. Beside, condensation of (*S*)-*tert*-butanesulfinamide with ketale cyclohexanone employing Ti(IV) salts at reflux temperature provided imine **2** in about 60–90% yields (Table 2). The carbonyl group of compound 1 is coordinated with Ti(IV) as a catalyst, which activates it towards nucleophilic attack of (*S*)-*tert*-butanesulfinamide. The imine was slowly hydrolysed on silica gel, so the column length of 8–10 cm was used with a flow rate such that the imine was eluted for 15 min. The imines were stored by placing a vial of the product into a container of drierite within a −20 °C freezer. In this step, this transformation could complete in 6 h (entry 2), and extending reaction time resulted in a decrease in yield (entries 3, 4, 8, 9). The investigation of various solvents was shown in Table 2 and THF was found to be the best choice. Titanium(IV) salts were next investigated, primarily to effect the condensation of TBSA with ketone. Due to their Lewis acidity and excellent water-absorbing ability, Ti(IV*)* salts such as $Ti(OEt)_4$ and $Ti(O\text{-}i\text{-}Pr)_4$ have been used and $Ti(OEt)_4$ gave the better yields.

The several factors contribute to the efficiency of current precedure: (1) (*S*)-*tert*-butanesulfinamide is available commercially in a pure state, also it is easily synthesized in two steps from inexpensive raw material; (2) (*S*)-*N*-*tert*-butanesulfinyl imines was formed from condensation of (*S*)-*tert*-butanesulfinamide and ketones in high yield; (3) the (*S*)-*N*-*tert*-butanesulfinyl imine actives for the nucleophilic addition of Grignard and (*S*)-*tert*-butanesulfinyl group acts as a powerful chiral inductive group; (4) the (*S*)-*tert*-butanesulfinyl group that acts as a Boc-surrogate is stable under basic conditions but may be easily cleaved with acid. In next step, addition reaction of Grignard reagent to *N*-sulfinylimine derived from 2-ketaled cyclohexanone (Scheme 3) was evaluated. Optimizing the reaction conditions was then carried out to improve both the yields and the diastereoselectivity of the reaction.

In addition, temperature was proved to be important for this reaction. An obvious increase in the yields was observed when the reaction temperature increased (up to 90%), but caused dramatic decrease in diastereoselectivity (entries 3, 4). It can be reasonably expected that equatorial attack were to occur on the lowest energy chair conformation, which has the ketal group located C2.

Scheme 3 Intermediates of nucleophilic addition to *N*-sulfinylimine

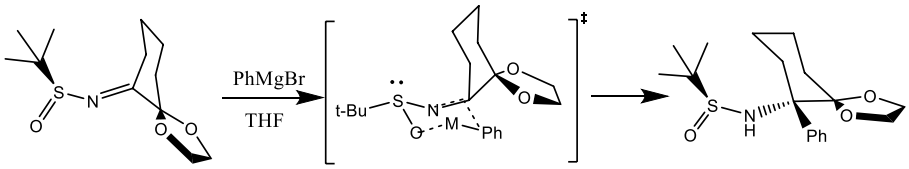
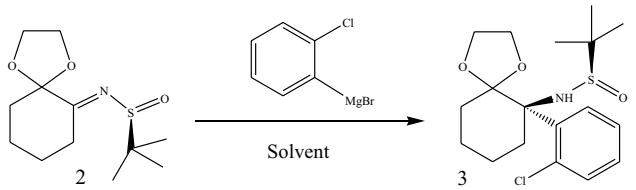


Table 3 Optimization of addition of Grignard reagent to *N-tert*-butanesulfinylimine 2



Entry	Solvent	*T* (°C)	Time (h)	Yield[a] (%)	dr[b] *S:R*
1	THF	−78	4	85	90:10
2	THF	−50	4	90	85:15
3	THF	0	4	95	78:22
4	THF	25	4	97	65:35
5	CH_2Cl_2	−78	4	55	94:6
6	Toluene	−78	4	65	88:12
7	Toluene	−78	8	64	85:25
8	Toluene	−50	4	80	70:30

[a]Isolated yield of material after chromatography

[b]Diastereomeric ratio was determined by chiral HPLC assay

As shown in Scheme 3, a six-membered cyclic transition state with Mg coordinated to the oxygen of the sulfinyl group is consistent with the sense of induction. In addition, the proposed cyclic transition state is consistent with the reaction proceeding with highest selectivities in noncoordinating solvents. Notably, the best diastereoselectivity (94: 6 dr) was obtained with CH_2Cl_2 as noncoordinating solvent, but along with low yield (55%, entry 5). The selectivity observed for Grignard reagent is also noteworthy, considering that transformation is performed in the coordinating solvent THF. Therefore, the best condition for Grignard addition was obtained in THF as solvent (entry 1, Table 3). In this model, Grignard reagent preferably added to the imine from the less hindered face to afford (S_s, *S*) as major diastereomer (Scheme 3).

The *N-tert*-butylsulfinyl group can act as not only an chiral auxiliary, but also an amine-protecting group. Then, using methyl iodide to provide easily the monomethylation and obtained desired product (4) with 70% yield [52–55]. Finally, the sulfinyl and ketale groups were removed from the compound (4) by brief treatment with stoichiometric quantities of HCl in a protic solvent to produce the ketamine (5) in 82% yield [30, 46, 49–51]. The enantiomeric excess was determined to be > 80% by HPLC analysis (DAICEL CHIRALCEL OD-H column).

Experimental

General

All the chemicals were used as purchased (Merck) for the reactions without further purification. All the organic solvents were purchased from commercial suppliers and were purified according to standard procedures. In addition, Lewis acids were obtained from commercial suppliers. All reactions were carried out in oven-dried glassware under nitrogen atmosphere. Infrared spectra were recorded using a Perkin-Elmer Spectrum-100 FT-IR spectrometer. IR spectra of liquids were recorded as thin films on NaCl plates. The ^{1}HNMR and ^{13}CNMR spectra were determined using TMS as an internal reference with an Avance FT NMR spectrometer operating at 250 and 60 MHz. The ^{13}CNMR spectra were determined using TMS as an internal reference with an Avance FT NMR spectrometer operating at 60 MHz. Mass spectra analyses were recorded on an Agilent Technologies, Model: 5975C VL MSD by EI mass spectrometry on a Q-TOF instrument. Preparative normal-phase HPLC was performed on a Waters HPLC prep 4000 system equipped with a 4000-controller pump using column DAICEL CHIRALCEL OD-H; detection: UV 254 nm, mobile phases were 5% 2-propanol/*n*-hexane, flow: 0.5 mL/min. Flash chromatography was performed using silica gel 60 (200–300 mesh). Thin-layer chromatography was carried out on silica gel 60 F-254 TLC plates of 20 cm × 20 cm. Column chromatography was performed using Merck Silica gel 60 (0.063–0.200 mm). Elemental analysis on C, H and N was performed using a Perkin-Elmer 2400 Elemental Analyser.

Synthesis of intermediates

Preparation of 1,4-dioxaspiro[4.5]decan-6-one (1)

A mixture containing of 1,2-cyclohexanedione (0.56 g, 5 mmol) in benzene (10 mL), ethylene glycol (0.31 g, 5 mmol) and p-toluenesulfonic acid (2 mg, 0.01 mmol) was

refluxed using a Dean–Stark apparatus for 18 h. Then, ether (20 mL) was added to the reaction mixture and diketone was extracted twice with 1 N NaOH solution (15 mL). The combined organic layer dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford the yellow oily product (yield 0.59 g, 75%). The crude product was used in the next reaction without further purification. IR (KBr): 3446 (OH), 2947, 2870, 1732, 1358, 1265, 1192, 1102, 1023, 952, 892, 804, 568 $cm^{-1;}$ ^1H NMR (250 MHz, $CDCl_3$, TMS) δ: 1.44–2.48 ppm (m, 8 H), 3.91 ppm (m, 4 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δC = 22.6, 26.1, 36.8, 39.5, 65.1, 106.7, 205.3 ppm. Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): [M+1] + 157 (13), [M] + 156 (27), 128 (35), 100 (31), 99 (100), 97 (32); elemental analysis for $C_8H_{12}O_3$: calculated C 61.52, H 7.74, found C 61.53, H 7.69%.

Preparations of (*S,E*)-2-methyl-*N*-(1,4-dioxaspiro[4.5]decan-6-ylidene)propane-2-sulfinamide (2)

A mixture containing **1** (0.312 g, 2 mmol), $Ti(OEt)_4$ (0.912 g, 4 mmol) in THF (20 mL) was reacted under a N_2 atmosphere. Then, (*S*)-*tert*-butanesulfinamide (0.27 g, 2.2 mmol) was added and the reaction mixture was refluxed for 6 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured into (20 mL) brine while rapidly stirring. The resulting suspension was filtered through a plug of Celite and the filter crude was washed with EtOAc (30 mL). The filtrate was transferred to a separatory funnel. The organic layer was washed with brine (3 10 mL). The brine layer was extracted with EtOAc (10 mL). Then, the combined organic layer dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The sulfinylimine 2 was purified by silica gel flash chromatography (1:3 EtOAc–hexane) (brown oil, yield 0.47 g, 90%). IR (KBr): 3340 (NH), 3253, 2952, 2873, 2714, 1668, 1620, 1579, 1455, 1363, 1311, 1188, 1096, 1048, 951, 891, 820 $cm^{-1.}$ ^1H NMR (250 MHz, $CDCl_3$, TMS) δ: 1.25 (s, 9 H), 1.32–2.53 (m, 8 H), 4.00 (m, 4 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$) δC: 22.1, 22.6, 26.2, 31.3, 37.3, 58.9, 64.7, 116.0, 182.6 ppm. α: + 153 (c 1.2 $CHCl_3$). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): [M] + 259 (3), 232 (7), 199 (22), 154 (19), 139 (16), 98 (47), 57 (100); elemental analysis for $C_{12}H_{21}NOS$: calculated C 55.57, H 8.16, N 5.40, found C 55.59, H 8.1, N 5.4%.

Preparation of (*S*)-*N*-((*S*)-6-argio-1,4-dioxaspiro[4.5]decan-6-(2-cholorophenyl)-2-methylpropane-2-sulfinamide (3)

A solution of imine **2** (0.22 g, 0.84 mmol) in dry THF (5 mL) at − 78 °C under N_2 was added dropwise from a dropping funnel to solution of 2-chlorophenyl magnesium bromide (0.38 g, 2 mmol) in 5 mL THF. The mixture was stirred at − 78 °C for 1 h. Then, the mixture reaction was warmed to room temperature for 4 h. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer was extracted twice with ether. The combined organic layer dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (1:3 EtOAc–hexane) to give the desired product as a yellow oil (yield 0.26 g, 85%). IR (KBr): 3310, 3257 (NH), 3059, 1310, 1189, 1097, 1048, 951, 893, 879, 751, 700 $cm^{-1.}$ ^1H NMR (250 MHz, $CDCl_3$, TMS) δ: 1.25 (s, 9 H), 1.33–2.32 (m, 8H), 3.58–3.64 (m, 1H), 4.15(m, 4 H), 6.86–7.78 (m, 4 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$) δC : 22.6, 23.6, 22.9, 28.82, 31.7, 38.6, 62.0, 65.8, 68.0, 122.3, 126.3, 128.7, 130.7, 131.0, 132.3, 133.6, 140.1 ppm. α: +179 (c 1.2 $CHCl_3$). de = 90% by HPLC analysis (DAICEL CHIRALCEL OD-H column). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): [M] + 371 (13), 344 (13), 336 (7), 311 (13), 266 (20), 239 (27), 191 (27), 57 (100); elemental analysis for $C_{18}H_{26}ClNO_3S$: calculated C 58.13, H 7.05, N 3.77, found C 58.22, H 7, N 3.77%.

Preparation of (*S*)-*N*-((*S*)-6-argio-1,4-dioxaspiro[4.5]decan-6-(2-cholorophenyl)-*N*,2-dimethylpropane-2-sulfinamide (4)

A solution of sulfinamide **3** (1 g, 2.7 mmol) in 20 mL acetone was homogenized at room temperature. Then, K_2CO_3 (1.11 g, 8.1 mmol) was added and the reaction mixture was refluxed for 2 h. Methyl iodide (1.52 g, 5.34 mmol) was added dropwise over 30 min. After the addition was completed, the mixture was stirred for 1.5 h. The mixture was filtered and concentrated under reduced pressure. The oil obtained was extracted twice with 25 mL *n*-hexane. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The product obtained was purified by silica gel column chromatography (2:2 EtOAc–hexane) (yellow oil, yield 1.45 g, 70%). IR (KBr): 3079, 2913, 2892, 1597, 1467, 1428, 1363, 1310, 1189, 1097, 1048, 951, 893, 879, 751, 700 $cm^{-1.}$ ^1H NMR (250 MHz, $CDCl_3$, TMS) δ: 1.25 (s, 9 H), 1.33–2.32 (m, 8H), 2.48 (s, 3H), 4.11–4.18 (m, 4 H), 6.86–7.78 (m, 4 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$) δC : 22.9, 23.5, 28.8, 31.8, 38.0, 38.9, 58.4, 63.5, 68.1,125.7, 127.8, 128.7, 130.3, 132.4, 140.7 ppm. α: +152 (c 1.2 $CHCl_3$). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): [M] + 385 (3), 371 (7), 311 (7), 266 (7), 251 (7), 206 (18), 111 (21), 98.2 (100), 84 (25), 55 (36); elemental analysis for $C_{19}H_{28}ClNO_3S$: calculated C 59.13, H 7.31, N 3.63, found C 59.22, H 7.27, N 3.63%.

Preparations of (*S*)-2-(2-cholorophenyl) 2-methylamino cyclohexan-1-one (*S*-ketamine) (5)

A solution of sulfinamide **4** (0.386 g, 1 mmol) in methanol (20 mL) was added slowly to 3.5 mL hydrochloric acid

(36%). The reaction mixture was stirred at 70 °C for 5 h. After completion of the reaction (monitored by TLC), the volatiles were removed under reduced pressure. Then, reaction mixture was cooled to 25 °C and was added 10 mL aqueous saturated $NaHCO_3$ solution was added. Next, ammonia was added dropwise to reach $PH = 6$. The amine obtained was extracted twice with 25 mL EtOAc and concentrated to pale yellow liquid. The combined organic layers were washed with brine and dried with anhydrous magnesium sulfate. Concentration under reduced pressure gave a residue, which was purified by flash silica gel chromatography (1:3 EtOAc–hexane) to afford the corresponding amine (*S*-ketamine), (yield 0.2 g, 82%). The enantiomeric excess was determined to be > 80% by HPLC analysis (DAICEL CHIRALCEL OD-H column). IR (KBr): 3050, 2842, 2624, 2624, 2555, 2428, 1723, 1597, 1467, 1428, 1363, 1310, 1189, 1097, 1048, 751 $cm^{-1.}$ ^1H NMR (250 MHz, $CDCl_3$, TMS) δ: 1.51–1.82 (m, 4H), 1.82–2.05 (m, 1H), 2.10 (s, 3H), 2.25–2.8 (m, 3H), 2.82–3.1 (m, 1H), 7.2–8.1 (4H) ppm. ^{13}C NMR (125.75 MHz, $CDCl_3$): δC = 23.8, 28.8, 30.4, 38.6, 39.7, 71.5, 127.6, 128.8, 130.3, 132.5, 134.4, 137.5, 208.0 ppm; Mp 123 °C; α: − 53.6 (c 2 EtOH) [56]. Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): [M] + 237 (12), 222 (28), 186 (24), 167 (28), 149 (100), 139 (44), 111 (44), 85 (72), 57 (64); elemental analysis for $C_{13}H_{16}ClNO$: calculated C 65.68, H 6.78, N 5.89, found C 65.82, H 6.75, N 5.9%.

Conclusions

We have presented a new strategy for the synthesis of (*S*)-ketamine as anesthesia drug. The synthetic strategy included the construction of a chiral nitrogen-substituted quaternary carbon center using an enantioselective 1,2-addition reaction of 2-cholorophenyl magnesium bromide to chiral α-*N*-sulfinylimine-ether acetal, having α-chiral sulfinylimine auxiliary. The use of (*S*)-*tert*-butanesulfinamide chiral auxiliary is one advantageous in the current strategy because the *tert*-butanesulfinyl group activates the imine for nucleophilic addition and serves as a powerful chiral inductive group. The chiral compound with a nitrogen-substituted quaternary carbon bearing α-carbonyl group was obtained after deprotection. Thus, the asymmetric synthesis of (*S*)-ketamine, after methylation and deprotection, was accomplished with 82% yield and 70% ee.

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