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Process Development on the Preparation of *trans*-(+)-2-Methylaminocyclohexanol: A Fascinating Resolution Example

Xinbo Lu,* Zunle Xu, and Guangming Tang

Beijing HSD Medicinal Research, Zhong Guan Cun Chuang Ye Building 1008, Shang-Di, Beijing, P.R. China, and Chemistry Department, Zhong Shan University, Guang Zhou, 135 Xingang Road, P.R. China

A new simple process is described to produce the highly optically pure single isomer *trans*-(+)-2-methylaminocyclohexanol [(+)-MAC] by mixing (+)-di-*p*-toluoyltartaric acid (DTTA) with (±)-MAC in an appropriate ratio, agitating at 60 °C for 30 min. After filtration and recovery by basification, a 99% ee (+)-MAC is obtained.

Introduction:

Single isomers of *trans*-(±)-2-methylaminocyclohexanol [(+)-MAC and (−)-MAC] are important intermediates for the preparation of nitrogen-containing cycloalkylaminoaryl derivatives for CNS disorder,[1b] analgesia agents,[1c] and antiarteriostenotic agents.[1a] They are also important chiral intermediates useful as ligands, chiral auxiliaries, or in other asymmetric synthetic applications.[2] The (±)-MAC was first prepared by reacting an aqueous methylamine with cyclohexene oxide in the Mousseron[3] method. Another method was reported in 1983 by Japanese chemists.[4,5] The major problems faced with this reaction were the high-pressure involved and that the excessive primary amine released into air would cause particular difficulty for scale up.

The resolution of (±)-MAC with (+)-tartaric acid required 5−7 recrystallizations[6] with a yield of approximately 8%. The current (+)-MAC development is a practical method to make (±)-MAC suitable for large-scale preparation

Results and Discussion

(±)-MAC Preparation. The test results in our lab indicated that 40% aqueous methylamine solution reacted with cyclohexene oxide quite readily under reflux condition as described in Scheme 1. No high pressure or special equipment was required as in previous examples.[4,5]

In our tests, 2.5 equiv of aqueous methylamine solution was added to 1 equiv of **1** in 95% ethanol and refluxed for 3 h, the conversion of **1** being over 97%. The dimer impurity caused by further reaction of MAC with the epoxide was less than 3%. The trace amount of **1** and methylamine residue could be easily removed during the distillation since they both have low boiling points. The (±) MAC was prepared in over 90% yield and purity above 95%.

Scheme 1

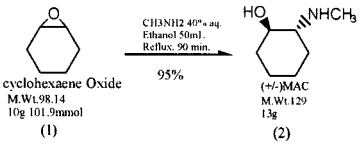

Table 1. **Solubility of salt (+)-MAC_2-(+)-DTTA versus (+)-MAC-(−)-DTTA**

crystalline	mp (°C)	solubility in H_2O (mg/mL)
(+)-MAC_2(+)-DTTA.	190−192	9
(+)-MAC(−)-DTTA	180−182	>2000

In our recent attempts on the (±)-MAC resolution, we obtained one crystalline solid with a structure of (+)-MAC_2-(+)-DTTA (by NMR) containing 100% pure (+)-MAC. The crystalline solid had very limited solubility in most solvents. Subsequently, we used 2 equiv of pure (+)-MAC mixed with 1 equiv of (+)-DTTA and 1 equiv of (−)-DTTA, respectively. The solubility test data on these solids is listed in Table 1.

From Table 1, the solubility of (+)-MAC-(−)-DTTA was 200 times more than that of (+)-MAC_2-(+)-DTTA, which provides a guideline for the efficient resolution.

When we reacted >4 equiv of (±)-MAC with 1 equiv of (+)-DTTA, most of the (+)-MAC_2-(+)-DTTA precipitated out owing to the very low solubility and left most of the other isomer with much higher solubility in the mother liquor. Once the reaction conditions favored the formation of the (+)-MAC_2-(+)-DTTA (a "eutectic" type solid) a good resolution could be obtained. The solvents were screened, and the best was ethanol, and actually the resolution efficiency was independent of the solvents used, when the other isomer salt of (−)-MAC-(+)-DTTA was with relatively high solubility and easily removed by adjusting the solvent volume. The resolution efficiency was even more easily achieved by running the resolution at 60 °C for 20 min, proving that the resolution efficiency was primarily dependent on the eutectic composition.

Table 2 shows the resolution examples with various molar ratios of (+)-DTTA over (±)-MAC.

The data listed in table were results from mixing various molar ratios of (±)-MAC to (+)-DTTA. The (±)-MAC and

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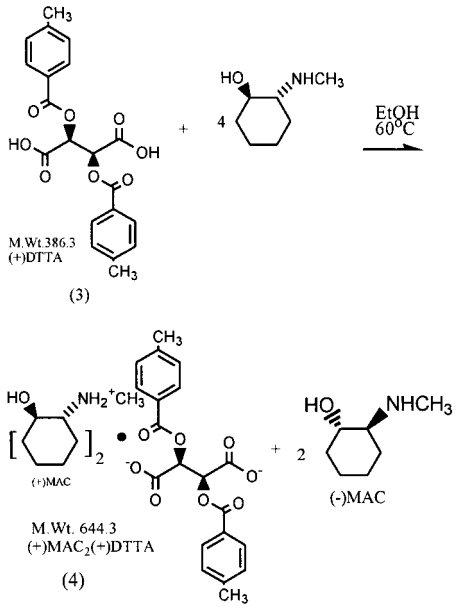
Table 2. **Resolution examples with various molar ratios of (+)-DTTA over (±)-MAC**

entry	(+)-DTTA (equiv)	(±)-MAC (equiv)	mp	ee (%)	*T* (°C)	(+)-MAC yield (%)
1	1	4	184	92.9	25	40.7
2	1	5	186	97.5	25	33.4
3	1	6	187	98.5	25	27.3
4	1	6	190	99.3	25	30.6
5	1	4	190	99.5	60	45.8
6	1	6	190	99.9	60	30.2

Scheme 2



(+)-DTTA were mixed in the correct molar ratio of 4:1, suspended in ethanol, agitated at 60 °C for 20 min, and then gradually cooled to room temperature and filtered. The crude product with optical purity >99%, chemical purity >99% was obtained in ∼45% yield.

The free base of (+)-MAC was recovered by agitating the (+)-MAC_2-(+)-DTTA salt in a mixture of aqueous 20% NaOH and TBME and then extracted back with TBME. After removal of TBME, the single isomer of (+)-MAC was obtained.

Conclusions

From the economic point of view, the **(±)**-MAC is much cheaper than (+)-DTTA and (−)-DTTA, without considering the recovery of (+)- or (−)-DTTA, and thus using 4 equiv of (±)-MAC with 1 equiv of (+)-DTTA at 60 °C to get an initial precipitate with ee > 99% gives the most efficient resolution with the best usage of the relatively expensive chiral reagent (Scheme 2).

Experimental Section

General Methods. Melting points are uncorrected.

IR spectra were recorded on an FT-IR spectrometer as thin films or KBr disks. ^{1}H and ^{13}C spectra were recorded at 250 and 63 MHz, using $CDCl_3$, CD_3OD, or D_2O as internal reference. Enantiopurities were determined by running a chiral HPLC test method. Chromatographic conditions: analytical column: Chiralpak AD, 25 cm × 4.6 mm (Daicel), mobile phase: hexane/2-propanol (85:15); column *T* °C = rt; flow rate: 1.0 mL/min; wavelength: 254 nm; run time: 20 min, sample preparation: precolumn derivation with *m*-toluoyl chloride.

***trans*-(±)-2-Methylaminocyclohexanol (2).** A mixture of **1** (500.0 g, 5094 mmol), methylamine (40% aqueous, 988.9 g, 12736 mmol), and ethanol (2500 mL) was mixed and heated to reflux for about 90 min. When the **1** residue was <1% by GLC, vacuum distillation was started at 60 °C. After removal of all the solvent and reactants, 650 g of a light yellow oil was obtained (yield > 95%, purity 95% by GC), bp 107−109/17 mm, FT-IR 3150 (bonded NH), 3320 (bonded OH) cm^{-1}; ^{1}HNMR (300 MHz) δ 0.93−1.02 (dd, 1H, J = 3.1,16.2), 1.18−1.32 (m, 3H), 1.68−1.72 (d, 2H, = 10) 1.95−2.22 (m, 3H), 2.39 (s, 3H), 3.18−3.26 (m, 1H), 3.4 (s, 1H). ^{13}C NMR (60 MHz) δ 24.5, 24.9, 29.5, 33.2, 33.8, 65.0, 73.5.

(+)-*trans*-2-Methylaminocyclohexanol (+)-Di-*p*-toluoyl-tartrate [(+)-MAC]$_2$-[(+)-DTTA] (4). In a three necked mL round-bottom flask equipped with a mechanic stirrer and a thermometer were charged 200 g of (+)-DTTA (517.7 mmol) and 600 mL of EtOH; the mixture then was heated to 45 °C, and then (±)-MAC (267.1 g, 2070.5 mmol) in 400 mL of ethanol was added dropwise in 15 min. The mixture was further heated to 60 °C and agitated for 30 min and then cooled gradually in about 30 min to 23 °C and agitated for another 20 min. The mixture was filtered, and a white solid was obtained and rinsed with 100 mL of ethanol twice. The white solid after being dried over vacuum at 45 °C for about 5 h was weighed: about 316.8 g (95%); purity >99%. $[\alpha]^{25}_D$ +69.5° (*c* 5, in H_2O); mp = 190−193 °C; FT-IR 3150 (bonded NH), 3320, 3000 (bonded OH), 1700 (C═O) cm^{-1}; ^{1}HNMR (250 MHz) δ 1.17−1.27 (m, 8H), 1.65−1.71 (m, 4H), 1.93−1.97 (m, 2H), 2.03−2.07 (m, 2H), 2.33 (s, 6H), 2.60 (s, 6H), 2.79−2.83 (m, 2H), 3.42−3.50 (m, m, 2H), 5.62 (s, 2H), 7.28−7.31 (d, 4H, J = 7.95),7.89−7.92 (d, 4H, J = 7.63); ^{13}C NMR (60 MHz) δ 23.6, 26.1, 28.4, 32.3, 36.2, 66.1, 72.9, 77.8, 128.8, 132.1, 132.7, 148.2, 170.1, 175.8.

***trans*-(±)-2-Methylaminocyclohexanol (5). 4** (300 g, 465.5 mmol) was mixed with TBME (1200 mL, 50% (wt/wt)), NaOH (82.0 mL, 1025 mmol), and water (1000 mL). The mixture was stirred at rt for 3 h to get a clear heterogeneous solution when standing still. After phase separation, the aqueous phase was extracted with TBME (1000 mL) three times. The combined organic phase was washed with brine and then concentrated into a white solid: 117.6 g (yield: 98%); purity > 99%. $[\alpha]^{25}_D$ +89.5° (*c* 5, in H_2O); FT-IR 3150 (bonded NH), 3320 (bonded OH) cm^{-1}; $_1$HNMR (300 MHz) δ 0.93−0.99 (dd, 1H, J = 2.7, 11.9), 1.18−1.32 (m, 3H), 1.67−1.72 (d, 2H, J = 12.5), 1.92−2.21 (m, 3H), 2.39 (s, 3H), 3.18−3.26 (m, 1H), 3.67 (s, 1H); ^{13}C NMR (60 MHz) δ 24.5, 24.9, 25.7, 29.5, 33.2, 33.8, 65.0, 73.5

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