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An improved synthesis and resolution of *cis*- and *trans*-2,3-diphenyl morpholines

Ravindra S. Jagtap, Navalkishore N. Joshi *

Division of Organic Chemistry, National Chemical Laboratory, Pune 411 008, India

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ABSTRACT

An improved procedure for the synthesis of *cis*- and *trans*-2,3-diphenyl morpholines with good overall yield is described. The stereoisomers were efficiently resolved through the corresponding diastereomeric salts using tartaric acid and (*R*)-mandelic acid.

1. Introduction

Substituted morpholine derivatives are the core of various natural products and biologically active compounds.[1] This class of compound has found important applications in pharmaceuticals[1,2] and in agricultural use.[3] Chiral morpholine derivatives have found numerous applications in asymmetric synthesis as chiral auxiliaries[4] as well as chiral ligands.[5] Various methods are known in the literature for the synthesis of morpholine derivatives.[1,6] In most of the methods reported, the morpholine ring is constructed via the reaction of chiral 1,2-amino alcohols with various electrophiles such as chloroacetyl chloride,[7] epoxides,[8] activated alkenes[9] and others.[10] Over the course of our work on asymmetric catalysis,[11] we wanted to use morpholine ligands **1** and **2** (Fig. 1). Although the preparation of the two stereoisomers of these molecules is known, we found the procedure to be unsatisfactory in terms of yield. Also, the reported rotations were incorrect. Herein we report an optimized preparation of (±)-**1** and (±)-**2** which were then efficiently resolved.

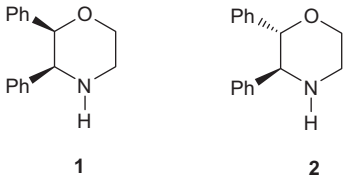
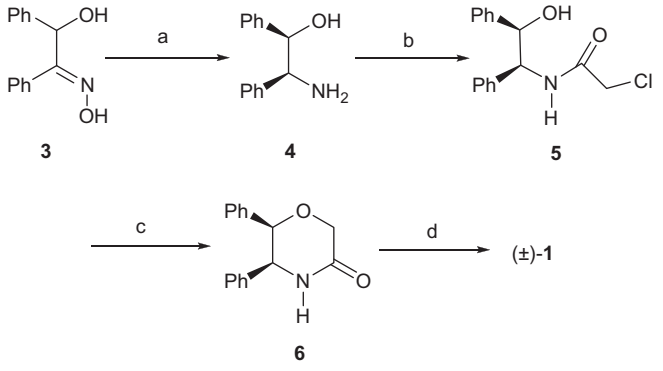


Figure 1.

2. Results and discussion

2.1. Preparation of (±)-1 and (±)-2

Both the *cis*- and *trans*-2,3-diphenyl morpholines can be accessed from a common intermediate, *erythro*-2-amino-1,2-diphenylethanol **4**. The amino alcohol **4**[12] was prepared by hydrogenation of α-benzoin oxime **3** (Scheme 1). Our initial efforts to construct the morpholine ring using a one step protocol[13] by condensation of **4** with 1,2-dibromoethane or ethylene-di-*p*-toluenesulfonate were unsuccessful. We therefore decided to investigate the reported syntheses of these molecules. Stefanovsky et al. reported the syntheses of the title compounds **1** and **2** in 14% and 23% overall yields starting from homochiral aminoalcohols **4** and **7**, respectively.[14a] In asymmetric synthesis, it is always desirable to introduce the chirality in the last possible step. We therefore decided to redesign the reported procedure for **1** and **2**. In order to improve the yield, *erythro* amino alcohol **4** was reacted with chlorocetyl chloride at −10 °C in the presence of $NaHCO_3$ using methanol as the solvent. Racemic *erythro*-2-(chloroacetylamino)-1,2-diphenylethanol **5** was obtained as the sole product in a 98% yield (Scheme 1). With-



Scheme 1. Reagents and conditions: (a) H_2-Pd/C, MeOH; (b) $ClCH_2COCl$, $NaHCO_3$, MeOH; (c) KOH, EtOH; (d) $LiAlH_4$, THF.

* Corresponding author. Tel.: +91 20 25902055; fax: +91 20 25902629.
E-mail address: nn.joshi@ncl.res.in (N.N. Joshi).

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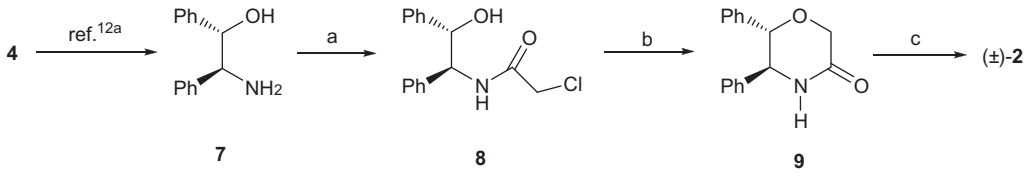
out further purification, **5** was cyclized to *cis*-5,6-diphenylmorpholin-3-one **6** in a 97% yield using potassium hydroxide in ethanol at reflux. The ^{1}H NMR of the unpurified **6** was clean and showed no isomerization at the stereocenters under reflux conditions. The cyclization of **5** to **6** can also be carried out by using sodium hydride or potassium *tert*-butoxide in *N,N*-dimethyl formamide or *tert*-butanol, respectively, with similar yields. Compound **6** was reduced with $LiAlH_4$ in THF under reflux for 16 h to obtain racemic *cis*-2,3-diphenyl morpholine **1** in overall 59% yield from **4** without applying column chromatographic purification. Further purification was better achieved through oxalate salt rather than the reported hydrochloride method. After the usual work-up, the crude compound was then treated with oxalic acid (0.5 equiv) to give the oxalate salt, which was subsequently recrystallized from ethanol and basified with aqueous NaOH to give (±)-**1** in a 62% yield. These modified reaction conditions were successfully scaled up to 100 mmol. An overall yield of 59% yield was achieved starting from **4**.

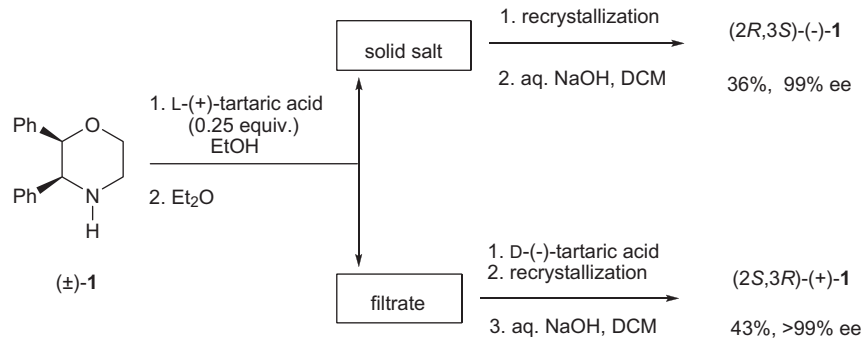
After the successful optimization of the reaction conditions, we used this protocol for the preparation of racemic *trans*-2,3-diphenylmorpholine **2** (Scheme 2). The racemic *threo*-2-amino-1, 2-diphenylethanol **7** was obtained from **4** according to the literature.[12a] Following the above described reaction conditions, **7** was converted to (±)-**2** in 56% overall yield.

2.2. Resolution

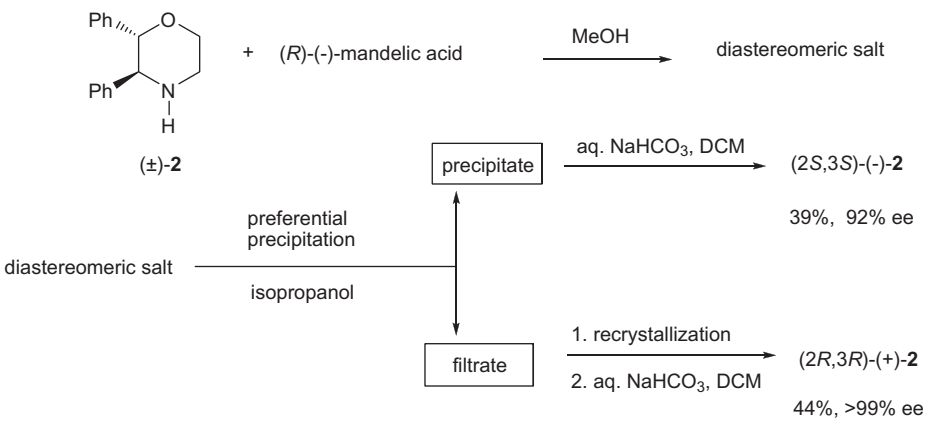
The most practical method for the resolution of racemic amines is the preparation of diastereomeric salt with an optically active acid, and then separation via crystallization.[15] To the best of our knowledge, the resolution of **1** and **2** is not known in the literature. Initial examination of various resolving agents, such as (−)-glutamic acid, (1*R*)-(−)-camphorsulphonic acid, (−)-menthoxyacetic acid and (−)-mandelic acid proved unsuccessful. (−)-Pyroglutamic acid or (+)-*O*-acetyl mandelic acid provided resolution, but required multiple crystallizations. Finally, the resolution of (±)-**1** was accomplished through the sequential use of L- and D-tartaric acid. It was observed that the stoichiometry of the resolving agent affected the yield as well as the enantiomeric excess. When (±)-**1** and L-(+)-tartaric acid were used in a 1:0.5 ratio, (−)-**1** and (+)-**1** were isolated in 39% and 42% yields with 94% and 72% ee, respectively. A ratio of 1:1 did not provide any resolution at all. The best results were obtained when a ratio of 1:0.25 was used



Scheme 2. Reagents and conditions: (a) $ClCH_2COCl$, $NaHCO_3$, MeOH/THF; (b) KOH, EtOH; (c) $LiAlH_4$, THF.



Scheme 3. Resolution of *cis*-2,3-diphenyl morpholine **1**.



Scheme 4. Resolution of *trans*-2,3-diphenyl morpholine **2**.

(Scheme 3). In an optimized protocol, (±)-**1** and L-(+)-tartaric acid (0.25 equiv) were mixed in ethanol and stirred overnight. The solid tartrate salt was separated from the unreacted morpholine through extraction with ether. Subsequent recrystallization of the salt from ethanol and basification gave (−)-**1**. The (+)-enantiomer was obtained from the mother liquor by similar treatment with D-(−)-tartaric acid. Both of the enantiomers were obtained in good yields and high enantiomeric purity after a single crystallization of the corresponding tartrate salts. The enantiomeric purity of both enantiomers was found to be ⩾99% by chiral HPLC. The solvent played a crucial role in the resolution process as revealed by the fact that racemic **1** was obtained when the salt was prepared in methanol.

In order to resolve the corresponding racemic *trans*-2,3-diphenyl morpholine **2**, we first tried L-(+)-tartaric acid. However, we could only isolate one enantiomer in very low yield with 95% ee. Success was achieved when using (−)-mandelic acid as the resolving agent (Scheme 4). The diastereomeric salt was prepared by mixing the acid and racemic **2** in methanol. However we were unable to separate the diastereomeric salts by recrystallization. The preferential precipitation[11c] method resulted in clean separation.

The resulting solid was dissolved in boiling isopropanol and then stirred at room temperature for 2 h followed by filtration. The purified salt, after basification, gave (−)-**2**. The mother liquor from the aforementioned resolution process was evaporated to dryness and the solid was crystallized from ethyl acetate. Subsequent basification of the salt provided (+)-**2**. The enantiomeric purity was determined by chiral HPLC. We observed higher specific rotation for the *cis*- as well as *trans*-isomers as compared to the known values reported in the literature[14a] (see Section 4).

3. Conclusion

In conclusion, we have prepared all four stereoisomers of 2,3-diphenyl morpholine in excellent overall yields. The resolution of *cis*-2,3-diphenyl morpholine was accomplished with high enantiomeric purity through the sequential use of L- and D-tartaric acid. Resolution of the *trans*-isomer was achieved using (−)-mandelic acid. The evaluation of these ligands in the enantioselective addition of organozinc reagents to aldehydes is currently in progress.

4. Experimental

4.1. General

All solvents and reagents were purified and dried according to the literature procedures.[16] The reactions were monitored by TLC using silica gel 60 F_{254} pre-coated plates. The products were purified by column chromatography on silica gel (100–200 or 230–400 mesh). All melting points were recorded on a Büchi B-540 electro thermal melting point apparatus and are uncorrected. Optical rotations were measured on Bellimheam+Standley ADP220 digital polarimeter. IR spectra were recorded on a Shimadzu FTIR-8400 spectrophotometer. ^{1}H spectra were recorded at 200 MHz with TMS as the internal standard. ^{13}C NMR spectra were recorded at 50 MHz with $CDCl_3$ (δ = 77) as the reference. Micro analysis was performed using a Carlo-Erba CHNS-0 EA 1108 elemental analyzer. All compounds provided satisfactory spectroscopic data. The enantiomeric excess was determined using a chiral column on HPLC.

4.2. (±)-*Erythro*-2-amino-1,2-diphenylethanol 4

A solution of racemic α-benzoin oxime **3** (11.36 g, 50 mmol) in methanol (130 mL) was hydrogenated at room temperature and at 50 psi pressure using 10% Pd/C (0.5 g) for 6 h. The usual work-up[12b] provided a crude solid (10.13 g, 95%). Recrystallization of the solid from methanol gave racemic *erythro*-2-amino-1,2-diphenylethanol **4** as white crystals. Yield: 8.53 g (80%); mp 163–165 °C (lit.[12a] 163 °C).

4.3. (±)-*Erythro*-2-(chloroacetylamino)-1,2-diphenylethanol 5

A two liter round-bottomed flask equipped with a magnetic stirrer bar and an addition funnel was charged with **4** (10.67 g, 50 mmol), $NaHCO_3$ (12.6 g, 150 mmol) and methanol (700 mL). The assembly was cooled to −10 °C. Freshly distilled chloroacetyl chloride (4.4 mL, 55 mmol) was added dropwise through the addition funnel over 1 h and the mixture was gradually allowed to warm to room temperature and stirred for a further 2 h. The procedure was repeated by the addition of additional chloroacetyl chloride (5.6 mL, 70 mmol) in three portions. The reaction mixture was stirred at room temperature for 24 h. Methanol was then removed on a rotary evaporator. The residue was suspended in water (300 mL) and stirred for 15 min. The reaction mixture was then filtered and dried to give **5** as a white solid, which was used for the next step without any purification. Yield: 14.18 g (98%); mp 193–194 °C (lit.[14a] 187–188 °C).

4.4. (±)-*cis*-5,6-Diphenylmorpholin-3-one 6

A two liter round-bottomed flask equipped with a magnetic stirrer bar and a reflux condenser was charged with crude **5** (28.97 g, 100 mmol), KOH (8.41 g, 150 mmol) and ethanol (700 mL). The reaction mixture was stirred at reflux for 1.5 h, after which the mixture was allowed to cool to room temperature. Ethanol was then removed on a rotary evaporator. To the residue 0.5 M aqueous HCl (200 mL) was added and the mixture was extracted with dichloromethane (1 × 300 mL, 2 × 150 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give **6** as a white solid, which was used for the next step without any purification. Yield: 24.54 g (97%); mp 181–182 °C (lit.[14a] 177–179 °C).

4.5. (±)-*cis*-2,3-Diphenylmorpholine 1

An oven-dried one liter round-bottomed flask with a side arm equipped with a stirrer bar, addition funnel and a reflux condenser, was charged with $LiAlH_4$ (8.47 g, 223 mmol). The flask was cooled to 0 °C in an ice bath and 50 mL of freshly distilled anhydrous THF was added under an argon atmosphere. To the resulting suspension, a solution of **6** (20.42 g, 80.61 mmol) in THF (600 mL) was added dropwise over a period of 2.5 h. After the addition, the ice bath was removed and the mixture was heated at reflux for 16 h. The reaction mixture was cooled to 0 °C, diluted with diethyl ether (200 mL) and quenched cautiously by the dropwise addition of 1 M NaOH (50 mL). The white solid was removed by filtration. The filtrate was dried over Na_2SO_4 and concentrated under reduced pressure to obtain a crude sticky mass (14.06 g), which was then dissolved in ethanol (400 mL) and treated with oxalic acid·$2H_2O$ (3.7 g, 0.5 equiv) and filtered. The resulting oxalate salt after recrystallization from ethanol followed by basification with aqueous NaOH gave (±)-**1**. Yield 12 g (62%); White solid; mp 82–84 °C (lit.[14b] 82–84 °C).

4.6. Resolution of (±)-1

To a solution of L-(+)-tartaric acid (1.5 g, 10 mmol) in ethanol (30 mL) was added a solution of (±)-**1** (9.57 g, 40 mmol) in ethanol (160 mL) and the resulting mixture was stirred overnight at room temperature. Ethanol was then removed on a rotary evaporator at 40 °C. To the residue, diethyl ether (150 mL) was added and the mixture was stirred for 1 h. Filtration of the reaction mixture provided the tartrate salt (6.52 g), which was recrystallized from

ethanol (90 mL) to obtain white crystals 4.53 g (36%); mp 181–184 °C; $[\alpha]_D^{25} = -19.0$ (*c* 0.42, MeOH). The second isomer of the morpholine was isolated from the mother liquor. To improve the yield, the mother liquor from the ethanol solution was basified with aqueous NaOH and gave free morpholine, which was mixed with the mother liquor from the ether solution. The combined free morpholine (6.18 g, 25.82 mmol) was then treated with D-(−)-tartaric acid (1.91 g, 12.72 mmol) in ethanol as described above. The resulting tartrate salt, after recrystallization from ethanol, provided white crystals 5.4 g (43%); mp 182–185 °C; $[\alpha]_D^{25} = +19.7$ (*c* 0.44, MeOH). Basification of the salt was carried out using aqueous NaOH to provide the corresponding enantiomerically pure morpholines in quantitative yield. Isomer (−)-**1** of the morpholine was obtained from the (−)-tartrate salt, while isomer (+)-**1** was obtained from the (+)-tartrate salt. (2*R*,3*S*)-(−)-**1**; Yield 36%: white solid; mp 73–75 °C. $[\alpha]_D^{25} = -77.2$ (*c* 2.59, $CHCl_3$) [lit.[14a] −28.3 (*c* 2.6, $CHCl_3$)]; 99% ee Kromasil-5-Amycoat column; *i*-PrOH/PE/TFA (20:80:0.1); 0.5 mL/min; 220 nm; major isomer: t_R = 7.76 min; minor isomer t_R = 9.34 min. (2*S*,3*R*)-(+)-**1**; Yield: 43%; white solid; mp 73–75 °C; $[\alpha]_D^{25} = +76.4$ (*c* 2.59, $CHCl_3$); >99% ee Kromasil-5-Amycoat column; *i*-PrOH/PE/TFA (20:80:0.1); 0.5 mL/min; 220 nm; minor isomer: t_R = 8.10 min; major isomer t_R = 9.04 min.

4.7. (±)-*Threo*-2-(chloroacetylamino)-1,2-diphenylethanol 8

The procedure described above for compound **5** was followed for **7** (14.78 g, 69.30 mmol), $NaHCO_3$ (17.44 g, 207.6 mmol), chloroacetyl chloride (12.5 mL, 156 mmol) and THF/MeOH (250 mL). Yield: 19.04 g (95%); white solid; mp 149–150 °C (lit.[14a] 147–148 °C).

4.8. (±)-*trans*-5,6-Diphenylmorpholin-3-one 9

The procedure described above for compound **6** was followed for **8** (21.34 g, 73.64 mmol), KOH (6.2 g, 110.5 mmol), EtOH (443 mL). Yield 17.37 g (93%); white solid; mp 185–187 °C (lit.[14a] 185–186 °C).

4.9. (±)-*trans*-2,3-Diphenylmorpholine 2

The same procedure described above for compound **1** was followed for **9** (3.6 g, 14.2 mmol), $LiAlH_4$ (1.34 g, 35.3 mmol) and THF (160 mL). Yield 2.17 g (64%); white solid; mp 85–87 °C; IR ($CHCl_3$): 3328, 3018, 2862, 1492, 1450 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.83 (bs s, 1H, NH), 3.0–3.13 (m, 1H), 3.27 (td, *J* = 11.5, 3.41 Hz, 1H), 3.77 (d, *J* = 8.84 Hz, 1H), 3.93 (td, *J* = 11.24, 2.65 Hz, 1H), 4.05–4.16 (m, 1H), 4.36 (d, *J* = 8.84 Hz, 1H) 6.95–7.20 (m, 10H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 46.5, 67.4, 67.9, 85.2, 127.3, 127.4, 127.5, 127.6, 127.8, 128.0, 139.0, 140.1 ppm; Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.29; H, 7.46; N, 5.90.

4.10. Resolution of (±)-2

To a solution of (±)-**2** (7.42 g, 31.03 mmol) in MeOH (120 mL) was added (*R*)-(−)-mandelic acid (4.73 g, 31.03 mmol) and the reaction mixture was stirred at room temperature for 1 h. Methanol was then evaporated on a rotary evaporator. The resulting salt was dissolved in boiling isopropanol (160 mL). The mixture was then allowed to cool to room temperature, stirred for 2 h, and filtered. The residue was washed with hot ethyl acetate to obtain one of the diastereomeric salts as a white precipitate (4.74 g, 39%); mp 175–177 °C; $[\alpha]_D^{25} = -116$ (*c* 1, MeOH). The second isomer of the salt was obtained from the mother liquor by evaporation followed by recrystallization from ethyl acetate (5.36 g, 44%); mp 150–151 °C; $[\alpha]_D^{25} = +32$ (*c* 1, MeOH). Basification of the salt was carried out using aqueous $NaHCO_3$ to provide the corresponding enantiomerically pure morpholines in quantitative yield. The isomer (−)-**2** of the morpholine was obtained from the precipitated salt while (+)-**2** was obtained from the salt left in the filtrate. (2*S*,3*S*)-(−)-**2**; yield: 39%; white solid; mp 74–76 °C; $[\alpha]_D^{25} = -100$ (*c* 2, $CHCl_3$); 92% ee Kromasil-5-Amycoat column; *i*-PrOH/PE/TFA (20:80:0.1); 0.5 mL/min; 220 nm; minor isomer: t_R = 9.06 min; major isomer t_R = 10.32 min. (2*R*,3*R*)-(+)-**2**; Yield 44%; white solid; mp 74–76 °C; $[\alpha]_D^{25} = +102$ (*c* 2, $CHCl_3$) [lit.[14a] +92.7 (*c* 2.2, $CHCl_3$)]; >99% ee Kromasil-5-Amycoat column; *i*-PrOH/PE/TFA (20:80:0.1); 0.5 mL/min; 220 nm; major isomer: t_R = 8.68 min; minor isomer t_R = 10.77 min.

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