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Dexmethylphenidate: An Efficient Process for the Racemization of Unwanted (2*S*,2′*S* or *l-threo*)-α-Phenyl-α-(2-piperidyl)acetamide

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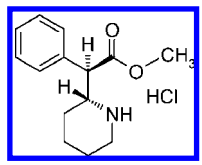
Abstract:

(2*R*,2′*R*)-*d-threo*-α-Phenyl-α-(2-piperidyl)acetamide (3), an advanced intermediate for dexmethylphenidate hydrochloride synthesis, is prepared by the resolution of *dl-threo*-α-phenyl-α-(2-piperidyl)acetamide (2) with dibenzoyl-*d*-tartaric acid in isopropanol with % yield and 99% ee. Although this process is efficient, there is a need to recycle the unwanted *l-threo*-amide and uncrystallized *d-threo*- amide from the mother liquor. The purpose of this study is 2-fold, first being the pollution issue to discard large amounts of unwanted isomer and the second to reduce the cost of (1). This aspect of recovery of unwanted isomer 4 formed the basic objective of this study. We have developed a new, simple, and cost-effective process for the racemization in which 4 was treated with potassium carbonate and *N*-chlorosuccinimide in DMF followed by treatment with DBU to afford the olefinic intermediate (5). Subsequent hydrogenation of the double bond provided *dl-erythro*-α-phenyl-α-(2-piperidyl)acetamide (6); the latter intermediate has already been converted into 1.

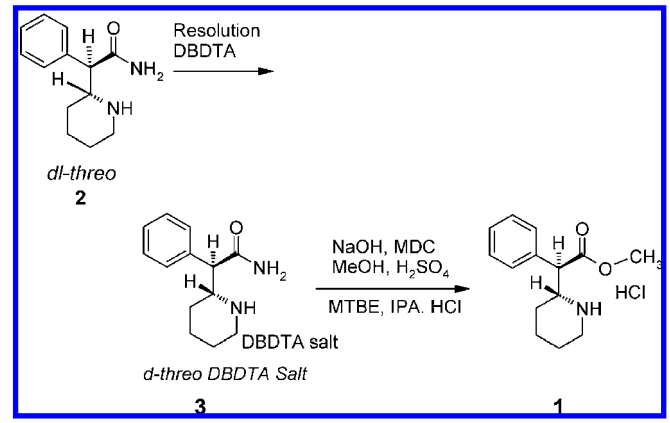
Introduction

Dexmethylphenidate hydrochloride **1,** a mild nervous system stimulant, is marketed in its racemic form essentially to treat children with attention deficit hyperactivity disorder (ADHD). Subsequent studies revealed that the (2*R*,2′*R*) or *d-threo*-isomer of methylphenidate is considerably more active than the corresponding (2*S*,2′*S*) or *l-threo*-isomer and this led to the introduction of dexmethylphenidate hydrochloride **1** into the consumer's market.[1,2]



The first synthesis of (2*R*,2′*R*)-methylphenidate hydrochloride **1**, reported in 1958 by Rometsch,[1,3] had utilized the resolution of *dl-erythro*-α-phenyl-α-(2-piperidyl)acetamide to obtain the enantiopure *l-erythro*-α-phenyl-α-(2-piperidyl)acetamide. The latter isomer was subjected to epimerization, hydrolysis and esterification to obtain *dl-threo*-methylphenidate. The concept of resolution of *dl-threo*-methylphenidate has been

Scheme 1



reported by several routes which include classical resolutions,[4−8] enzymatic hydrolysis[9,10] and enantioselective synthesis.[11−15] Recently, the synthesis of **1** has also been reported by Thai who utilized *d*-pipecolic acid as a chiral pool precursor.[16]

Khetani and Ramaswamy patented the resolution process of **2** (Scheme 1) by using dibenzoyl-*d*-tartaric acid in isopropanol. They also demonstrated the transformation of **3** to **1** with methanol and sulfuric acid.[17]

Results and Discussion

The resolution of (2*RS*,2′*RS* or *dl-threo*-α-phenyl-α-(2-piperidyl)acetamide **2** by using dibenzoyl-*d*-tartaric acid in

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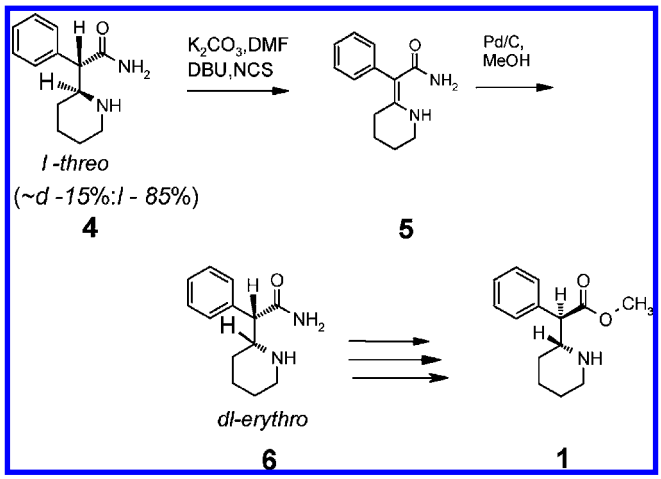
Scheme 2



isopropanol, as reported in the literature,[17] was successfully repeated in our laboratory to give (2*R*,2′*R*)-isomer **3** in quantitative yield. The analysis of the mother liquor after the resolution and basification of **3** by HPLC revealed that it contained typically the (2*R*,2′*R*)-isomer **3** in 15−20% and the unwanted (2*S*,2′*S*)-isomer **4** in 80−85%.

We believe that the most viable process of racemization of **4** would be to create a double bond across the two chiral centers as shown in scheme 2. The catalytic reduction of the double bond of **5** is expected to provide the *dl-erythro* isomer **6** by the virtue of *cis* reduction. The transformation of *dl* **6** to *dl-threo* **2** and subsequently to dexmethylphenidate **1** are well documented[17] (Scheme 2).

In order to install the double bond across the chiral centers of **4**, the advantage of the reactive benzylic carbon at C-2 was explored. The obvious choice would be halogenation at the C-2 carbon followed by dehydrohalogenation. The most suitable method[17] from scale-up and an economy point of view was *N*-chlorosuccinimide for chlorination and DBU for elimination.

Therefore, **4** was subjected to the reaction of *N*-chlorosuccinimide and potassium carbonate in DMF. This step was carefully monitored by TLC, and after 3 h, the reaction was complete. The isolation of generated chloro intermediate was avoided by *in situ* addition of DBU giving rise to the double bond intermediate **5**.

In order to optimize the elimination reaction, the organic bases such as piperidine, diisopropyl amine, triethylamine as well as inorganic bases such as KO*t*Bu, NaOH, and KOH were also attempted. However, with organic bases the reaction was found to be very sluggish, and most of the starting material **4** remained unreacted. With metal alkoxides, the elimination product was formed, but side reactions were also observed (Table 1).

The next investigation was to establish the optimal quantity of DBU to ensure maximum yield. We conducted many experiments (Table 2) and observed that 1.25 equiv of DBU (entry 3) produced best yield of **5**.

Our next target was the reduction of **5**. In the presence of Pd−C in methanol at 10 kg/cm^2 at 45 °C for 10 h, **5** gave the *dl-erythro* isomer **6**. Its HPLC analysis indicated that 0.28% of *dl-threo* isomer was also formed during the reduction step.

Table 1. **Study of various bases for formation of 5**

rxn	solvent	base	temp (°C)	time (h)	isolated yield (%)[a]
1	DMF	diisopropylamine	0−5 °C	3	no reaction
2	DMF	triethylamine	0−5 °C	3	no reaction
3	DMF	piperidine	0−5 °C	3	no reaction
4	DMF	NaOH	0−5 °C	3	37
5	DMF	KOH	0−5 °C	3	46
6	DMF	KO*t*Bu	0−5 °C	3	23

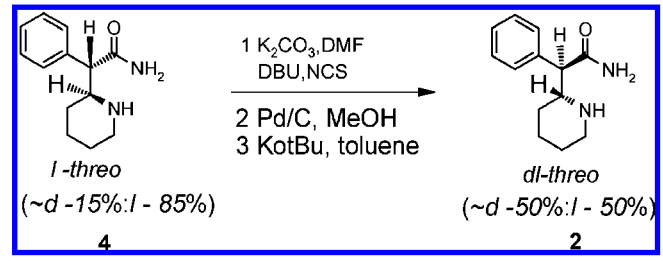
[a] Product was isolated by column chromatography over silica gel (60−120 mesh) using *n*-hexane and ethyl acetate (9.5:0.5).

Table 2. **Optimization of DBU for formation of 5**

rxn	mol equiv (DBU)	solvent	temp (°C)	time (h)	isolated yield (%)
1	0.25	DMF	0−5	3	54[a]
2	0.50	DMF	0−5	3	62[a]
3	1.25	DMF	0−5	3	82
4	1.70	DMF	0−5	3	83

[a] Product was isolated by column chromatography over silica gel (60−120 mesh) using *n*-hexane and ethyl acetate (9.5:0.5).

Scheme 3



Subsequently, **6** was converted to **2** by treatment with potassium *tert*-butoxide.

Conclusion

In conclusion we believe that we have developed a new, superior, and cost-effective method (Scheme 3) for racemization of **4** to **2**.

Experimental Section

All materials were purchased from commercial suppliers. Unless specified otherwise, all reagents and solvents were used as supplied by manufactures. The ^{1}H NMR spectra were recorded in CD_3OD and DMSO-d_6 on Varian 400 MHz; the chemical shifts were reported in δ ppm relative to TMS. The FT-IR spectra were recorded in the solid state KBr dispersion using Perkins Elemer FT-IR spectrophotometer. The mass spectra were recorded on Applied Biosystems API2000LCMS mass spectrometer. The melting points were determined by using Buchi apparatus. The solvents and reagents were used without purification. Contents of *dl-erythro* and *dl-threo* were recorded on HPLC on Inertsil C8 (250 mm × 4.6 mm) at 210 nm and eluted with buffer (2.72 g KH_2PO_4 in 1000 mL DM water and pH adjusted to 3.51 using orthophosphoric acid/acetonitrile (800:200). Content of *d* and *l* isomers of *threo*-amide were recorded on chiral HPLC on Chiralcel ODH (250 mm × 4.6 mm) at 210 nm and eluted with *n*-hexane/ethanol/TFA/triethyl amine (950:50:0.2:0.1). TLC was performed by

using silica gel as the stationary phase and methanol/chloroform (5:5) as the mobile phase.

Preparation of 2-Phenyl-2-piperidin-2-ylidene-acetamide (5). A mixture *l-thero*-α-phenyl-α-(2-piperidyl)acetamide **4** (containing ∼15% of *d-threo* amide, 0.500 kg, 2.31 mol) and dimethylformamide (3.0 L) was cooled to 0−5 °C. Potassium carbonate (0.100 kg, 0.720 mol) was added and after 0.5 h, *N*-chlorosuccinimide (0.428 kg, 3.20 mol) and DBU (0.439 kg, 2.88 mol) added. The reaction was stirred for additional 0.5 h at 0−5 °C and then warmed to 25−30 °C for 2 h. At this time, the absence of **4** (by TLC) was noted. It was cooled to 0−5 °C and diluted with DM water (2.5 L). Toluene (2.5 L) was introduced and stirred for 1 h. The layers were separated, and aqueous layer was two times extracted with toluene (2 × 1 L). Combined toluene layers were concentrated under vacuum at 50−55 °C to give 0.406 kg (82%) of **5**. Mp: 132−134 °C, IR (KBr): δ 3481, 3294, 2956, 1634, 1568, 1339 cm^{-1}, MS (*m/z)*: 172, 200, 217, 239, 344, 455, ^{1}H NMR (DMSO-d_6): δ 1.4−1.5(m, 2H) 1.50−1.60 (m, 2 H), 1.80−1.90 (t, 2 H), 3.1−3.2 (t, 2 H), 4.5−5.0 (s, 1H), 5.8−6.2 (s, 1H), 7.0−7.5 (m, 5 H), 10.3 (s, 1H). ^{13}C NMR (100 MHz, DMSO): δ 20.27, 22.51, 27.83, 41.12, 96.41, 127.42, 129.59, 132.95, 139.28, 158.61, 172.68. Anal. for $C_{13}H_{16}N_2O$ (after recrystallization): calcd C, 72.22; H, 7.40; N, 12.96. Found C, 72.35; H, 7.45; N, 13.02.

Preparation of *dl-erythro*-α-Phenyl-α-(2-piperidyl)acetamide (6). 2-Phenyl-2-piperidin-2-ylideneacetamide **5** (0.400 kg, 1.85 mol), 10% Pd/C (40 g) in methanol (4.0 L) were hydrogenated at 10.0 kg/cm2 pressure at 45 °C for 10 h. After absence of **5** (by TLC), it was cooled to 30 °C and filtered through hyflow supercel. The filtrate was concentrated under *vacuo* at 50−55 °C. Acetic acid (2.9 L) was added to the reaction mass, stirred for 30 min at 60 °C and concentrated under *vacuo* at 55−60 °C. Ethyl acetate (1.45 L) was added to the concentrated mass and cooled to 0−5 °C. The solid was filtered, washed with cold ethyl acetate (0.37 L) and dried at 50−55 °C. The solid was dissolved in DM water (1.0 L), cooled to 0−5 °C, and basified to pH 12−12.5 using 30% sodium hydroxide solution. The solid was filtered, washed with cold DM water (1.1 L), and dried at 50−55 °C to give 0.32 kg (79.5%) of **6** as a solid. Mp: 140−143 °C, IR (KBr): 3313, 3037, 2966, 2928, 2766, 1670, 1409, 1361, 1024 cm^{-1}, MS (*m/z)*: 219, 239, 241, 455, *dl-erythro*/*dl-threo* content by HPLC: 99.72%:0.28%.

Preparation of *dl-threo*-α-Phenyl-α-(2-piperidyl)acetamide (2). The above and predominantly *dl-erythro*-α-phenyl-α-(2-piperidyl)acetamide **6** (0.31 kg, 1.42 mol) and potassium *tert*-butoxide (0.426 kg, 3.79 mol) in toluene (7.75 L). The reaction was heated at 70−75 °C for 24 h. After absence of **6** (by TLC), it was cooled to 20−25 °C, and HCl solution (preparation: 0.620 L aq HCl in 1.55 L DM water) was introduced and further stirred for 1 h. The layers were separated, the aqueous layer was basified to pH 12.5 using 30% sodium hydroxide solution (∼0.70 potassium *tert*-butoxide (0.426 kg, 3.79 mol). The solid obtained was filtered, washed with DM water, and dried at 50−55 °C to give 0.25 kg (81%) of **2** as a solid. Mp: 173−175 °C (lit[1] mp, 173 °C), IR (KBr): 3283, 3035, 2951, 2931, 1679, 1397, 1360, 1031 cm^{-1}, MS (*m/z)*: 136, 219, 221, 241, 437, 473 ^{1}H NMR (CD_3OD): δ 0.9−1.3(m, 3H) 1.40−1.70 (m, 3H), 2.60−2.70 (dt, 1 H), 3.0−3.1 (d, 1 H), 3.1−3.2 (dt, 1 H), 3.3−3.4 (dt, 1H), 7.2−7.4 (m, 5 H), *dl-erythro*/*dl-threo* content by HPLC 0.60%:99.40%, *d-threo*/*l-threo* content by chiral HPLC: 50.34%:49.66%.

Acknowledgment

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Supporting Information Available

Additional characterization data of compounds **2**, **4**, **5**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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