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SHORT SYNTHESIS OF METHYLPHENIDATE AND ITS *p*-METHOXY DERIVATIVE

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Abstract: A short method for the preparation of racemic *threo*- and *erythro*-methylphenidate derivatives is described. Condensation between α-ethoxy carbamate **1** and silyl ketene acetals **2a-b** in the presence of TESOTf (20 mol%) afforded a 1.5:1 mixture of carbamates **3a-b/4a-b**. Hydrogenolysis in EtOH followed by treatment with 3N HCl/MeOH afforded the corresponding hydrochlorides **7a-b/8a-b** in good yields.

Methylphenidate hydrochloride (*Ritalin*, *2RS,3RS*-α-phenyl-2-piperidineacetic acid methyl ester hydrochloride,[1] **7a**) is a commonly prescribed mild nervous system stimulant used in the treatment of Attention Deficit Hyperactivity Disorders (ADHD) in children and used for the treatment of narcolepsy and depression in adults.[2-4]

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Methylphenidate is a dopamine reuptake blocker with stimulant properties that was first synthesized more than 50 years ago.[5] The stimulant properties reside in the *threo* isomer **7a** and methylphenidate is administered to patients as a racemic mixture of *threo* diastereomers.[6,7] It has also been reported that a mixture of racemic *threo*- and *erythro*-methylphenidates can be epimerized to pure *threo* racemates.[4,8]

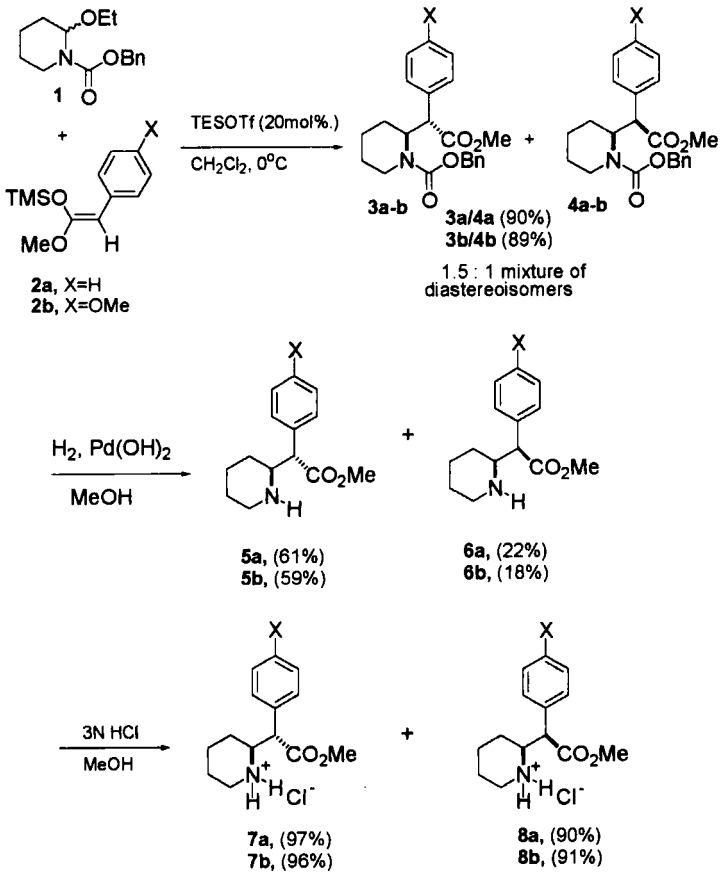
Although still marketed as a racemic mixture under the tradename Ritalin, drug companies are developing *2R,3R*-(+)-*threo*-methylphenidate, since it has been reported that the *2R,3R*-(+)-*threo*-methylphenidate is more active than the corresponding enantiomer, *2S,3S*-(-)-*threo*-methylphenidate.[8] Very recently, Prashad *et al.* reported an enzymatic resolution of (+/-)-*threo*-methylphenidate with α-chymotrypsin to afford *2S,3S*-(-)-*threo*- and *2R,3R*-(+)-*threo*-methylphenidate hydrochlorides in high enantiomeric purities.[9]

RESULTS AND DISCUSSION

We present herein a method for the preparation of a racemic mixture of *threo*- and *erythro*-methylphenidates[10] and its *p*-methoxy derivatives starting from α-ethoxy carbamate **1** and silyl ketene acetals **2a-b** (X= H, OMe), both prepared according to literature methods.[11,12]

Condensation between α-ethoxy carbamate **1** and silyl ketene acetals **2a-b** in CH_2Cl_2 at -78°C in the presence of TESOTf (20 mol%) afforded a 1.5:1 mixture of carbamates **3a-b/4a-b**, that were not separated.[13]

Hydrogenolysis of the mixtures (H_2, $Pd(OH)_2$, MeOH) afforded a mixture of *threo*- and *erythro* methylphenidates and its *p*-methoxy derivatives **5a-b/6a-b**, in moderate yields. The mixtures of **5a-b/6a-b** were separated by flash chromatography and treatment of each isomer separated with 3N HCl in MeOH afforded the corresponding hydrochlorides **7a-b** and **8a-b** in good yields. *Threo*- and *erythro* methylphenidate and its *p*-methoxy derivatives were characterized by comparison of their spectroscopic data (^{1}H- and ^{13}C-NMR and infrared spectra) with those reported by Perel [3] and Deutsch [4a].



We described here a very short and efficient synthesis of *threo*- and *erythro*-methylphenidates and its *p*-methoxy derivatives, starting from readily available and easily accessible starting materials.

EXPERIMENTAL

All experiments were carried out under an argon atmosphere in flame-dried glassware. Dichloromethane and diisopropylamine were distilled from CaH_2. TLC plates were obtained of silica gel 60 and GF (5-40 mm thickness) and visualization was accomplished with either a UV lamp or I_2 staining. ^{1}H-NMR

spectra were recorded on a Brucker AC 300/P (300 MHz) or Varian Gemini (300 MHz) spectrometer. Chemical shifts are recorded in ppm with the solvent resonance as the internal standard (deuterochloroform: δ 7.26). Data are reported as follows: chemical shift, multiplicity, (s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, st = sextet, br = broad, m= multiplet, dd = doublet of doublets, dt = doublet of triplets, br d = broad doublet, ddd = doublet of doublet of doublets), integration, coupling constants (Hz), and assignment. ^{13}C-NMR spectra were recorded on a Bruker AC 300/P (75 MHz) or Varian Gemini (75 MHz) spectrometer with complete proton decoupling. Chemical shifts are recorded in ppm with the solvent resonance as the internal standard (deuterochloroform: δ 77.00). IR spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. Chromatography on silica gel (230-400 mesh) was performed using a forced-flow of the indicated solvent system (flash cromatography).

EXPERIMENTAL:

***Threo-* and *Erythro*-methylphenidates:** Triethylsilyltrifluoromethanesulfonate (0.068 g, 0.059 mL, 0.26 mmol) is added to a stirred solution of α-ethoxy carbamate **1** (0.350 g, 1.33 mmol) and silyl ketene acetals **2a** (0.591 g, 2.66 mmol) in CH_2Cl_2 (3 mL) cooled to 0 °C in an argon atmosphere. The stirred solution is maintained at 0 °C for 1 h and let to stirr at rt for an additional 30 min, at which time it was quenched with saturated aqueous NH_4Cl (2.5 mL). The organic phase was extracted with CH_2Cl_2 (3 x 10 mL), the organic extract dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel (4% EtOAc/hexanes) affording an unseparable mixture of **3a** and **4a** (0.440 g, 1.2 mmol, 90%) as a colorless liquid. A suspension of **3a/4a** (0.440 g, 1.2 mmol) and $Pd(OH)_2$ on activated carbon (Pd 20%, 40 mg) in MeOH (50 mL) was stirred under an atmosphere of hydrogen for 30 minutes. After filtration, the mixture was evaporated and the crude product purified by flash chromatography on silica gel (10% EtOAc-hexanes) affording the diastereoisomers **5a** (0.170 g, 0.73 mmol, 61%) and **6a** (0.061 g, 0.264 mmol,

22%). A solution of **5a** (0.170 g, 0.73 mmol) in 3N HCl in MeOH (7 mL) was stirred at rt overnight. Evaporation under reduced pressure provided a white solid which was recrystallized from MeOH-EtOAc to give **7a** (0.191 g, 0.708 mmol, 97%). The same experimental procedure was used with **6a** (0.061 g, 0.264 mmol) to afford **8a** (0.064 g, 0.238 mmol, 90%).

(2*SR*)-2-[(*SR*)-1-methyloxycarbonyl-1-phenylmethyl)] hexahydropyridinium chloride, 7a: ^{1}**H-NMR (300MHz, CD_3OD):** δ 1.45 (m, 3H); 1.80 (m, 3H); 3.12 (td, J=12.6 and 3.2 Hz, 1H); 3.47 (dqt, J= 12.6 and 2.4 Hz, 1H); 3.74 (s, 3H); 3.85 (dt, J= 11.2 and 2.7 Hz, 1H); 3.92 (d, J= 10.0 Hz, 1H), 7.35 (m, 2H); 7.40 (m, 3H). ^{13}**C-NMR (75MHz, CD_3OD):** δ 22.8; 23.4; 27.7; 46.7; 53.4; 55.3; 59.2; 129,6; 129,7; 130,4; 135,2; 173,3. **IR:** 3450, 2950, 1737, 1636, 1429, 1148 cm^{-1}. **Melting Point:** 215.0-215.2 °C. **Anal. Calcd.** for $C_{14}H_{20}ClNO_2$: C (62.33%), H (7.47%), N (5.19%); Found: C (61.42%), H (7.68%), N (5.28%).

(2*SR*)-2-[(*RS*)-1-methyloxycarbonyl-1-phenylmethyl)] hexahydropyridinium chloride, 8a: ^{1}**H-NMR (300MHz, CD_3OD):** δ 1.70 (m, 3H); 1.90 (m, 3H); 2.10 (m, 1H); 3.00 (td, J=12.5 and 2.7 Hz, 1H); 3.30 (br s, 1H); 3.71(s, 3H); 3.80 (m, 1H); 3.95 (d, J= 9.0 Hz, 1H), 7.45 (m, 5H). ^{13}**C-NMR (75MHz, CD_3OD):** δ 23.0; 23.3; 28.8; 47.0; 53.2; 55.9; 59.5; 130.0; 130.3; 130.8; 134.0; 172.6. **IR:** 3433, 3036, 1723, 1578, 1331, 1166 cm^{-1}. **Melting Point:** 219.4-219.8 °C. **Anal. Calcd.** for $C_{14}H_{20}ClNO_2$: C (62.33%), H (7.47%), N (5.19%); Found: C (61.67%), H (7.81%), N (5.25%).

***Threo-* and *Erythro*-methylphenidate *p*-methoxy derivatives:** Triethylsilyltrifluoromethanesulfonate (0.068 g, 0.059 mL, 0.26 mmol) is added to a stirred solution of α-ethoxy carbamate **1** (0.350 g, 1.33 mmol) and silyl ketene acetals **2b** (0.671 g, 2.66 mmol) in CH_2Cl_2 (3 mL) cooled to 0 °C in an argon atmosphere. The stirred solution is maintained at 0 °C for 1 h and let to stirr at rt for an additional 30 min, at which time it was quenched with saturated aqueous NH_4Cl (2.5 mL). The organic phase was extracted with CH_2Cl_2 (3 x 10 mL), the organic extract dried ($MgSO_4$) and evaporated. The crude product was purified by

flash chromatography on silica gel (4% EtOAc/hexanes) affording an unseparable mixture of **3b** and **4b** (0.453 g, 1.18 mmol, 89%) as a colorless liquid. A suspension of **3b/4b** (0.453 g, 1.18 mmol) and $Pd(OH)_2$ on activated carbon (Pd 20%, 40 mg) in MeOH (50 mL) was stirred under an atmosphere of hydrogen for 30 minutes. After filtration, the mixture was evaporated and the crude product purified by flash chromatography on silica gel (10% EtOAc-hexanes) affording the diastereoisomers **5b** (0.183 g, 0.696 mmol, 59%) and **6b** (0.056 g, 0.212 mmol, 18%). A solution of **5b** (0.183 g, 0.696 mmol) in 3N HCl in MeOH (7 mL) was stirred at rt overnight. Evaporation under reduced pressure provided a white solid which was recrystallized from MeOH-EtOAc to give **7b** (0.200 g, 0.668 mmol, 96%). The same experimental procedure was used with **6b** (0.056 g, 0.212 mmol) to afford **8b** (0.058 g, 0.193 mmol, 91%).

(2*SR*)-2-[(*SR*)-1-(4-methoxyphenyl)-1-methyloxycarbonylmethyl] hexahydropyridinium chloride, 7b: ^{1}**H-NMR (300MHz, CD_3OD):** δ 1.60 (m, 6H); 3.08 (td, J=12.5 and 3.7 Hz, 1H); 3.43 (d, J= 12.5, 1H); 3.72 (s, 3H); 3.75 (m, 1H); 3.80 (br s, 4H), 6.94 (d, J = 8.8 Hz, 2H); 7.20 (d, J = 8.8 Hz, 2H). ^{13}**C-NMR (75MHz, CD_3OD):** δ 22.8; 23.4; 27.7; 46.6; 53.3; 54.56; 55.8; 59.4; 115.8; 126.9; 130.7; 161.5; 173.6 ppm. **IR:** 3445, 2952, 1735, 1640, 1430, 1160 cm^{-1}. **Melting Point:** 208.7-209.0 °C. **Anal. Calcd.** for $C_{15}H_{22}ClNO_3$: C (60.10%), H (7.40%), N (4.67%); Found: C (59.47%), H (7.65%), N (4.66%).

(2*SR*)-2-[(*RS*)-1-(4-methoxyphenyl)-1-methyloxycarbonylmethyl] hexahydropyridinium chloride, 8b: ^{1}**H-NMR (300MHz, CD_3OD):** δ 1.60 (m, 3H); 1.90 (m, 2H); 2.10 (m, 1H); 2.96 (dt, J=12.5 and 3.3 Hz, 1H); 3.27 (d, J = 11.0 Hz, 1H); 3.69 (s, 3H); 3.75 (m, 1H); 3.81 (br s, 4H), 7.00 (d, J = 8.8 Hz, 2H); 7.31 (d, J = 8.8 Hz, 2H). ^{13}**C-NMR (75MHz, CD_3OD):** δ 22.9; 23.3; 28.9; 46.9; 53.1; 55.2; 55.8; 59.6; 116.3; 125.7; 131.7; 162.1; 173.1. **IR:** 3435, 3030, 1726, 1580, 1350, 1180, 1170 cm^{-1}. **Melting Point:** 207.3-207.8 °C. **Anal. Calcd.** for $C_{15}H_{22}ClNO_3$: C (60.10%), H (7.40%), N (4.67%); Found: C (59.57%), H (7.46%), N (4.76%).

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