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A PRACTICAL ONE-POT SYNTHESIS OF WEINREB-LIKE AMIDES OF (S)- AND (R)-N-BOC-PIPECOLIC ACIDS FROM (±)-PIPERIDINE-2-CARBOXYLIC ACID

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Weinreb-like amides of (S)- or (R)-N-Boc-pipecolic acids (**5a**, **5b**; Scheme 1) have been frequently used as starting materials in the synthesis of biologically active compounds (e. g. IKK- β inhibitors,¹ glyt1 and/or glyt2 inhibitors,² PAR-1 antagonists,³ nAchR ligands,⁴ potential anticonvulsants,⁵ methylphenidate for treatment of ADHD,⁶ nAChRs agonist⁷). We report here a simple and economical route to obtain these valuable chiral building blocks starting from (±)piperidine-2-carboxylic acid (**1c**) using a one-pot method.

Amides **5a** and **5b** were easily prepared from the appropriate *N*-Boc acids (**4a** and **4b**) and *N*,*O*-dimethylhydroxylamine hydrochloride as described in the literature.⁸ As coupling agent, BOP/TEA⁶ or NMM/HOBt/WSC⁴ may be used. *N*-Boc-Pipecolic acid enantiomers (**4a** and **4b**) are commercially available (*e. g.* from Aldrich) or could be prepared from optically active aminoacids **1a** and **1b** with *N*-protection with a Boc-group. The Boc-protection was performed in different ways such as with $Et_3N/MeOH/Boc_2O$;⁶ Boc-ON/ $Et_3N/acetone/water⁵$ and $Boc_2O/Et_3N/dioxane/water.⁹$ Pipecolic acid enantiomers (**1a** and **1b**) may be purchased from suppliers (*e.g.* Aldrich) at a rather high price, or can be prepared from **1c** by resolution with tartaric acid enantiomers.⁵ The diastereomeric tartarate salts were recrystallized and subjected to ion-exchange chromatography on an Amberlite IR-120 column. The crude products obtained were recrystallized again to afford pure optically active acids. By the use of the above method (-)-(*S*)-and (+)-(*R*)-pipecolic acids were obtained from **1c** in 44 and 48% yield, respectively.

In the course of our studies, it was found that recrystallization of the diastereomeric tartarate salts could be eliminated if the hot solution during the resolution is seeded with optically pure tartarate salt **3a** or **3b**, respectively (*see Experimental Part*). As a more important modification, it was found that tartarate salts of (S)- or (R)-pipecolic acids proved to be suitable

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materials for the *N*-Boc-protection without isolation of the free aminoacids on Amberlite column. The *N*-protection was performed with $Boc_2O/Et_3N/dioxane/water$ (rt, 24 h) and the tartaric acid could then be removed during the work-up of the reaction mixture *via* simple aqueous extraction. Pure **4a** was isolated with column chromatography in excellent yield (96%). The optical purity was determined by comparing its optical rotations with that published earlier. The physical and spectroscopic data of our sample were identical with those reported in the literature (*see Experimental Section*).



A further significant shortcut was achieved when crude 4a was used as starting material for the formation of amide 5a without purification by column chromatography. 1,1-Carbonyldiimidazole (CDI) was used to activate the *N*-protected acid which was then allowed to react with *N*,*O*-dimethylhydroxylamine hydrochloride (DMF, rt, overnight). Pure end-product 5a was isolated by column chromatography. The total yield of 5a calculated on the (*S*)-enantiomer content of 1c is about 56%. This modified one-pot procedure afforded 5a in high yield and in a



simple and economical way; two isolation steps using column chromatography (Amberlite resin, silica) could be eliminated by this procedure. (*R*)-Enantiomers 4b and 5b could be prepared in an identical way; however, in the first step, resolution of 1c should be performed with L-(+)-tartaric acid (2b) to yield salt 3b, which could be transformed 4b or 5b as described above.

We found an alternative and economical procedure which utilizes the mother liquor obtained in the resolution of 1c with 2a (to prepare (*S*)-products). The mother liquor, containing mainly enantiomer 1b from 1c as D-(-)-tartarate salt (3c), was evaporated to dryness and then treated with $Boc_2O/H_2O/Et_3N/dioxane$ to afford crude *N*-Boc product 4c with $[\alpha]_D^{25}$ from +36° to +45° (c = 2.0, CH₂Cl₂), depending on the effectiveness of the original resolution. The obtained 4c was treated with L-(+)-tartaric acid (2b) in aqueous acetone containing a small amount of HCl (24 h reflux), whereupon *N*-deprotection and resolution took place in the same step affording the pure (*R*)-acid as its tartarate salt 3b (59% calculated from the (*R*)-enantiomer content of 1c). Salt 3b thus obtained, could be transformed into 4b (87%) or directly into 5b (53%) without purification of 4b by applying our one-pot method.

As Weinreb amides **5a** and **5b** have rather low $[\alpha]_D^{25}$ values $\{e.g. lit.^6 [\alpha]_D^{25}$ for **5a** is +1.88° (c = 4.3, CH₂Cl₂), for **5b** -1.35° (c = 2.89, CH₂Cl₂)}, the optical purity of our products could not be determined on the basis of their specific rotation and comparison with literature data. Although the measurement of our samples in CH₂Cl₂, gave ambiguous results, more congruent data were obtained in MeOH {**5a**: $[\alpha]_D^{25} = +1^\circ$ (c = 4.0, CH₂Cl₂), $[\alpha]_D^{25} = -14.2^\circ$ (c = 5.0, MeOH); **5b**: $[\alpha]_D^{25} \approx -2.5^\circ$ (c = 2.0, CH₂Cl₂), $[\alpha]_D^{25} = +14.8^\circ$ (c = 5.98, MeOH)}. Therefore to check their optical purity amides **5a** and **5b** were transformed into known compounds with more characteristic optical rotations. Amides were allowed to react with phenyllithium solution to yield ketones **6a** and **6b**. Specific rotation of **6a** and **6b** obtained from **5a** and **5b** {**6a**: $[\alpha]_D^{25} = -24.6^\circ$ (c = 2.0, CH₂Cl₂); **6b**: $[\alpha]_D^{25} = +27.0^\circ$ (c = 1.99, CH₂Cl₂); **6b**: $[\alpha]_D^{25} = +25.8^\circ$ (c = 1.06, CH₂Cl₂)} thus proving the high *ee* value of our synthetic intermediates **5a** and **5b**.



Applications of **5a** and **5b** to the synthesis of complex and/or biologically active compounds are in progress.

EXPERIMENTAL SECTION

Solvents were purified using standard procedures (MeOH: Grignard-reaction, acetone: $KMnO_4$, Et₄N: KOH, dioxane: Na + benzophenone). Column chromatography was performed with silica

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gel (Merck 60 and Merck-9385). Analytical thin-layer chromatography was performed with silica gel plates (Merck, TLC silica gel 60 F_{254}), and the plots were visualized under UV light or developed in iodine atmosphere and/or immersion in a solution of *a*-toluidine or with ninhydrin solution. Melting points were obtained on a Carl Zeiss apparatus equipped with microscope. IR data were recorded as KBr discs on a Nicolet-7795 FT-IR spectrometer. Optical rotations were measured on an AA-10R automatic polarimeter (Optical Activity Ltd.) using 1.0 dm cells and on sodium D line (589 nm) at 25°C. MS spectra were run on a ZAB 2SEQ mass spectrometer. ¹H and ¹³C NMR measurements were carried out on a Varian Gemini 200 spectrometer.

(-)-(S)-2-Carboxypiperidinium (2S,3S)-3-carboxy-2,3-dihydroxypropanoate (3a).- To a stirred, hot and mildly opalescent solution of 1c (160 g, 1.24 mol) in MeOH (960 mL) (-)-D-tartaric acid {(2a, 180 g, 1.2 mol; $[\alpha]_D^{25} = -14.2^\circ$ (c = 10.3, H₂O)} was added; the solution became a little more opalescent. The mixture was diluted with a further portion of MeOH (100 mL) and a small quantity (*ca*. 0.5 g) of pure recrystallized salt 3a { $[\alpha]_D^{25} = -20.5^\circ$ (c = 2.0, H₂O)} was added as seeds. The mixture became clear for a few seconds then formation of crystals started to appear from the hot solution. The mixture was cooled to rt over about 1 h, then the mixture was refrigerated for overnight. The crystal mass was collected, washed with cold MeOH (250 mL, in portions) to yield 3a (143.8 g, 83%), as colorless crystals, mp. 194-198°C, $[\alpha]_D^{25} = -20.5^\circ$ (c = 2.0, H₂O); *lit.*⁵ mp 194-196°C, *lit.*⁵ $[\alpha]_D^{25} = -19.5^\circ$ (c = 2.0, H₂O).

The mother liquor was evaporated in vacuo to dryness to afford 3c as an oil.

(+)-(R)-2-Carboxypiperidinium (2R,3R)-3-carboxy-2,3-dihydroxypropanoate (3b).

Boc protection.- Salt **3c** {50 g, about 180 mmol; $[\alpha]_D^{25} = -14.2^\circ$ (c = 10.3, H₂O)} was dissolved in a mixture of dioxane (220 mL), H₂O (52.5 mL) and Et₃N (65.0 mL) at rt, then Boc₂O (54.2 g, 248 mmol) was added and the mixture stirred for 24 h. The dioxane was evaporated under reduced pressure. The residue was poured into a cold mixture of AcOEt (3.0 L) and 0.5 N HCl solution (760 mL). After extraction, the organic phase was washed with cold water (2 x 400 mL), and dried. The filtrate was evaporated under reduced pressure. The related was poured under reduced pressure. The crude product was purified with column chromatography (eluent: CHCl₃, then CHCl₃ + MeOH, 20/1) to yield **4c** (23.5 g) as white crystals, mp. 198-200°C, $[\alpha]_D^{25}$ = from +36 to +45° (c = 2.0, CH₂Cl₂).

Deprotection and Resolution in One Step.- To a solution of **4c** (60 g, 261 mmol) in a mixture of H_2O (116 mL), acetone (30 mL) and 1N HCl solution (5.0 mL) **2b** (39.1 g, 261 mmol) was added and the mixture was refluxed for 24 h. To the hot solution acetone (100 mL) and a small amount of pure **3b** as seeding were added.

A further portion of acetone (500 mL) was added until the cloud point. The mixture was cooled to rt then refrigerated overnight. The precipitated crystals were collected, washed with a mixture of acetone and water (100 mL + 30 mL) and acetone (60 mL) to yield **3b** (43.2 g, 59%) as a colorless crystal mass, mp. 195-196°C, $[\alpha]_D^{25} = +20.0^\circ$ (c = 1.99, H₂O); *lit.*⁵ mp. 195-196°C, *lit.*⁵ $[\alpha]_D^{25} = +21^\circ$ (c = 2.0, H₂O).

(-)-(*S*)-1-(*tert*-Butoxycarbonyl)piperidine-2-carboxylic Acid (4a).- To a solution of 3a (10.0 g, 35.8 mmol) in a mixture of dioxane (45 mL), water (12 mL) and Et₃N (13.5 mL) di-*tert*-butyl dicarbonate (Boc₂O; 11.2 g, 51.2 mmol) was added in dioxane (10 mL) at rt. The reaction mixture was stirred for 24 h at rt, then the dioxane was evaporated under reduced pressure. The residue was poured to a cold mixture of AcOEt (0.5 L) and 0.1 N HCl solution (150 mL). After extraction, the organic phase was washed with cold water (2 x 100 mL), dried and evaporated under reduced pressure. The crude product was purified with column chromatography (eluent: CHCl₃ then CHCl₃ + MeOH, 20/1) to yield 4a (7.8 g, 96%) as colorless crystals, mp. 121-123°C, $[\alpha]_D^{25} = -57.2^\circ$ (c = 2.0, CH₂Cl₂), $[\alpha]_D^{25} = -43.2$ (c = 1.0, MeOH), $[\alpha]_D^{25} = -61.2^\circ$ (c = 0.99, AcOH); *lit.*⁶ mp. 123-124°C, *lit.*⁶ $[\alpha]_D^{25} = -58.7^\circ$ (c = 3.42, CH₂Cl₂). Spectroscopic characterization (¹H, ¹³C NMR, IR) resulted in identical data with those reported in refs. 6 and 7. It is worth mentioning that due to hindered amide rotation in the NMR spectra some duplication of proton and carbon peaks can be observed.

(+)-(*R*)-1-(*tert*-Butoxycarbonyl)piperidine-2-carboxylic Acid (4b).- Salt 3b (5.5 g, 19.7 mmol) was transformed into 4b as described above [dioxane (25 mL), water (7.0 mL) and Et₃N (7.5 mL) di-*tert*-butyl dicarbonate (6.2 g, 28.4 mmol)] to yield 3.92 g (87%) of white crystals, mp. 122-124°C, $[\alpha]_D^{25} = +58.8^\circ$ (c = 1.66, CH₂Cl₂); *lit.*⁶ mp. 123-124°C, *lit.*⁶ $[\alpha]_D^{25} = +59.5^\circ$ (c = 2.06, CH₂Cl₂).

(+)-(S)-tert-Butyl 2-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (5a).- Two parallel runs were performed from **3a** (2 x 65.0 g; 2 x 0.232 mol) without purification of the N-Boc protected compound (4a). The protection was performed as described above in both charges affording 68.0 and 70.0 g crude 4a, respectively. Each crude product was dissolved separately in DMF (475 mL), CDI (40 g, 0.246 mol) was added and the mixture was stirred at rt for 2 h then N,O-dimethylhydroxylamine hydrochloride (25.0 g, 0.256 mol) was admixed in portions. Both mixtures were stirred further for 3 h at rt then left to stand overnight. The solvent was evaporated under reduced pressure and the residues from the two charges were combined and purified by column chromatography (adsorbent: Merck 60, 1 kg; eluent: hexane then hexane + AcOEt, 75/25). In the course of the chromatography three fractions were collected: A) 27 g (with a little contamination); B) 39 (pure fraction); C) 17 g (with a little contamination). The first and third fractions were collected and purified again to afford 37.8 g pure colorless oil. Yield: 76.8 g (56%) - after three steps: resolution, N-protection and formation of amide. $[\alpha]_D^{25} \approx +1^\circ$ (c = 4.0, CH₂Cl₂), $[\alpha]_{D}^{25} = -14.2^{\circ}$ (c = 5.0, MeOH); *lit.*⁶ $[\alpha]_{D}^{25} = +1.88^{\circ}$ (c = 4.3, CH₂Cl₂). The spectroscopic data (¹H, ¹³C NMR, MS) were identical with those reported.^{4,6,7} (The ¹H and ¹³C NMR spectra of 5a showed similar peak-duplications as acid 4a).

(-)-(*R*)-tert-Butyl 2-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (5b).- In the first step 3b (31.4 g, 112.5 mmol) was allowed to react with Boc₂O (33.9 g, 155.3 mmol) in dioxane

(145 mL), water (38.0 mL) and Et₃N (42.0 mL) as described above. The crude *N*-Boc derivative (**4b**, 29.1 g) obtained was dissolved in DMF (180 mL), followed by addition of CDI (20.5 g, 126 mmol). The mixture was stirred at rt for 2 h then *N*,*O*-dimethylhydroxylamine hydrochloride (12.65 g, 130.3 mmol) was added in portions. The mixture was stirred for a further 3 h at rt then left to stand overnight. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (eluent: hexane + AcOEt, 6/4) to afford **5b** as pure colorless oil (16.4 g, 53%). $[\alpha]_D^{25} = -2.5^\circ$ (c = 2.0, CH₂Cl₂), $[\alpha]_D^{25} = +14.8^\circ$ (c = 5.98, MeOH); *lit*.⁶ $[\alpha]_D^{25} = -1.35^\circ$ (c = 2.89, CH₂Cl₂).

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