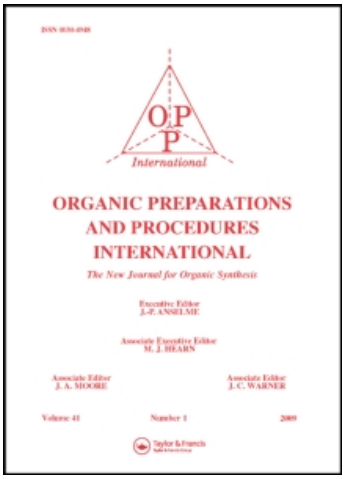

Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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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To cite this Article Moldvai, István , Dömyei, Gábor , Temesvári-Major, Eszter and Szántay, Csaba(2007) 'A PRACTICAL ONE-POT SYNTHESIS OF WEINREB-LIKE AMIDES OF (*S*)- AND (*R*)-*N*-BOC-PIPECOLIC ACIDS FROM (+)-PIPERIDINE-2-CARBOXYLIC ACID', Organic Preparations and Procedures International, 39: 5, 503 — 508
To link to this Article: DOI: 10.1080/00304940709458602
URL: http://dx.doi.org/10.1080/00304940709458602

ORGANIC PREPARATIONS AND PROCEDURES INT., 39 (5), 503-508 (2007)

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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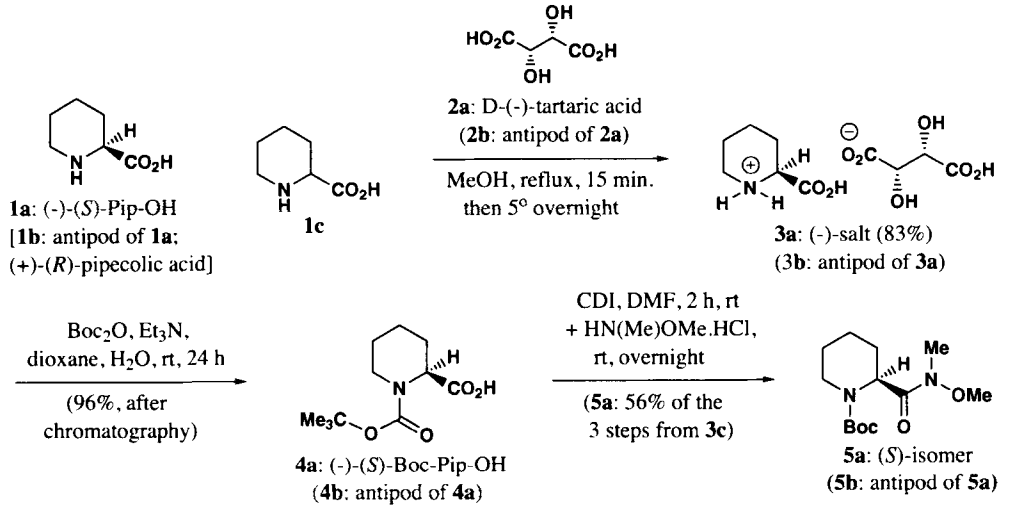
Weinreb-like amides of (*S*)- or (*R*)-*N*-Boc-pipecolic acids (**5a**, **5b**; *Scheme 1*) have been frequently used as starting materials in the synthesis of biologically active compounds (*e. g.* IKK-β inhibitors,[1] glyt1 and/or glyt2 inhibitors,[2] PAR-1 antagonists,[3] nAchR ligands,[4] potential anti-convulsants,[5] methylphenidate for treatment of ADHD,[6] nAChRs agonist[7]). 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/TEA[6] or NMM/HOBt/WSC[4] 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/water[5] 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.

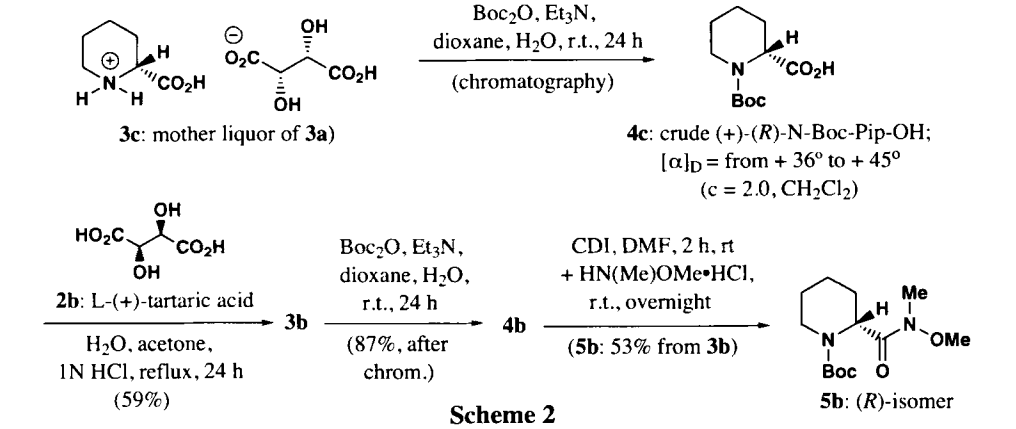
In the course of our studies, it was found that recrystallization of the diastereomeric tartarate salts could be eliminated if the hot solution during the resolution is seeded with optically pure tartarate salt **3a** or **3b**, respectively (*see Experimental Part*). As a more important modification,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

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*).



Scheme 1

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

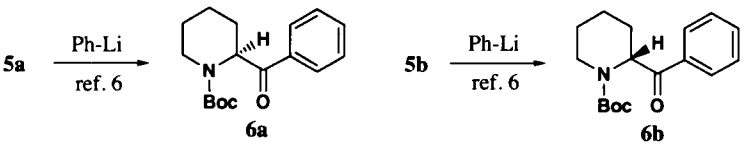


Scheme 2

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, CH_2Cl_2), 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, CH_2Cl_2), for **5b** -1.35° (c = 2.89, CH_2Cl_2)}, 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 CH_2Cl_2, gave ambiguous results, more congruent data were obtained in MeOH {**5a**: $[\alpha]_D^{25}$ = +1° (c = 4.0, CH_2Cl_2), $[\alpha]_D^{25}$ = -14.2° (c = 5.0, MeOH); **5b**: $[\alpha]_D^{25} \approx$ -2.5° (c = 2.0, CH_2Cl_2), $[\alpha]_D^{25}$ = +14.8° (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° (c = 2.0, CH_2Cl_2); **6b**: $[\alpha]_D^{25}$ = +27.0° (c = 1.99, CH_2Cl_2), respectively} are in good agreement with published data[6] {**6a**: $[\alpha]_D^{25}$ = -24.6° (c = 2.03, CH_2Cl_2); **6b**: $[\alpha]_D^{25}$ = +25.8° (c = 1.06, CH_2Cl_2)} thus proving the high *ee* value of our synthetic intermediates **5a** and **5b**.



Preparation of Ketones (6a, 6b) from Amides (5a, 5b)

Scheme 3

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: $KMnO_4$, Et_3N: KOH, dioxane: Na + benzophenone). Column chromatography was performed with silica

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 ^{13}C 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° (c = 10.3, H_2O)} 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° (c = 2.0, H_2O)} 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° (c = 2.0, H_2O); *lit.*[5] mp 194-196°C, *lit.*[5] $[\alpha]_D^{25}$ = -19.5° (c = 2.0, H_2O).

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

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

Boc protection.- Salt **3c** {50 g, about 180 mmol; $[\alpha]_D^{25}$ = -14.2° (c = 10.3, H_2O)} was dissolved in a mixture of dioxane (220 mL), H_2O (52.5 mL) and Et_3N (65.0 mL) at rt, then Boc_2O (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 crude product was purified with column chromatography (eluent: $CHCl_3$, then $CHCl_3$ + 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, CH_2Cl_2).

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° (c = 1.99, H_2O); *lit.*[5] mp. 195-196°C, *lit.*[5] $[\alpha]_D^{25}$ = +21° (c = 2.0, H_2O).

(-)-(*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 Et_3N (13.5 mL) di-*tert*-butyl dicarbonate (Boc_2O; 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: $CHCl_3$ then $CHCl_3$ + MeOH, 20/1) to yield **4a** (7.8 g, 96%) as colorless crystals, mp. 121-123°C, $[\alpha]_D^{25}$ = -57.2° (c = 2.0, CH_2Cl_2), $[\alpha]_D^{25}$ = -43.2 (c = 1.0, MeOH), $[\alpha]_D^{25}$ = -61.2° (c = 0.99, AcOH); *lit.*[6] mp. 123-124°C, *lit.*[6] $[\alpha]_D^{25}$ = -58.7° (c = 3.42, CH_2Cl_2). Spectroscopic characterization (^1H, ^{13}C 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 Et_3N (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° (c = 1.66, CH_2Cl_2); *lit.*[6] mp. 123-124°C, *lit.*[6] $[\alpha]_D^{25}$ = +59.5° (c = 2.06, CH_2Cl_2).

(+)-(*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. $[\alpha]_D^{25} \approx +1°$ (c = 4.0, CH_2Cl_2), $[\alpha]_D^{25}$ = -14.2° (c = 5.0, MeOH); *lit.*[6] $[\alpha]_D^{25}$ = +1.88° (c = 4.3, CH_2Cl_2). The spectroscopic data (^1H, ^{13}C NMR, MS) were identical with those reported.[4,6,7] (The ^1H and ^{13}C 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 Boc_2O (33.9 g, 155.3 mmol) in dioxane

(145 mL), water (38.0 mL) and Et_3N (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° (c = 2.0, CH_2Cl_2), $[\alpha]_D^{25}$ = +14.8° (c = 5.98, MeOH); *lit.*[6] $[\alpha]_D^{25}$ = -1.35° (c = 2.89, CH_2Cl_2).

Acknowledgements.- Financial support by *Grants 1/A/005/2004 NKFP Medichem2 (Hungary)* is gratefully acknowledged. Special thanks are due to *Dr. Ágnes Gömöry* for the MS spectra, *Mrs. Gabriella Hanák* and *Mrs. Mónika Jeruska* for technical assistance.

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(Received May 4, 2007; in final form July 6, 2007)