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EFFICIENT SYNTHETIC METHOD FOR L-TARTARAMIDES BY AMINOLYSIS OF REACTIVE 2,3-*O*-ISOPROPYLIDENE-L-TARTARYL CHLORIDE

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ABSTRACT: The reactive 2,3-*O*-isopropylidene-L-tartaryl chloride **4** was firstly synthesized from L-(+)-tartaric acid. Various chiral 2,3-*O*-isopropylidene-L-tartaramides **5** were prepared by aminolysis of the reactive L-tartaryl chloride **4** with primary and secondary amines.

Naturally occurring L-(+)-tartaric acid has been utilized in wide range of synthetic organic fields as chiral synthon or chiral auxiliary specially in asymmetric synthesis.[1,2] In the course of studies developing new kinds of chiral macrocyclic ligands, an efficient amidation on L-tartaric acid derivatives with various primary and secondary amines was required for synthesis of macrocyclic tetraamides in high dilution reaction condition. Although the known *N,N,N',N'*-tetramethyl-L-tartaramide was prepared from aminolysis of its ester with dimethyl amine in

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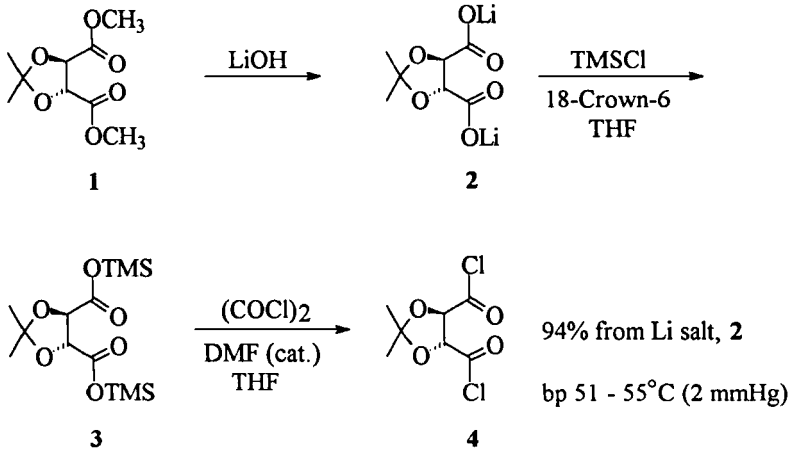
elevated temperature and concentrated reaction condition,[3] the general synthetic methods for forming amide bonds from carboxylic acid derivatives such as carboxylic acids, esters and anhydrides with amines are not efficient enough for high dilution cyclization reactions. The reactive acid halides are often used for the high dilution macrocyclization forming ester bonds or amide bonds. Tartaric acid halides are desired, but have not been yet reported for these reactions.

The polar carboxyl and hydroxyl groups in tartaric acid must be protected to transform it into the reactive tartaryl chloride **4** in organic solvents. Readily available dimethyl 2,3-*O*-isopropylidene-L-tartrate **1**[4] is chosen for the purpose. To transform carboxylate ester functionality into carboxylic acid chloride, the base-catalyzed hydrolysis of dimethyl ester **1** in methanolic aqueous lithium hydroxide gave tartrate lithium salt **2**. With neutral phase transfer catalyst, 18-crown-6, the dried lithium salt **2** suspended in THF was converted to bis(trimethylsilyl) tartrate **3** which is stable and homogeneous in reaction condition.[5] The heterogeneous suspension became clear solution as the trimethylsilyl ester **3** was formed. The labile trimethylsilyl ester **3** in THF was treated with oxalyl chloride and catalytic amount of DMF to give 2,3-*O*-isopropylidene-L-tartaryl chloride **4**. The analytically pure tartaryl chloride **4** was obtained by vacuum distillation in overall yield 94% from the lithium salt **2** (Scheme 1). The white icy acid chloride **4** was characterized by elemental analysis, IR[6], ^{1}H and ^{13}C NMR spectroscopy. The tartaric acid anhydride, a possible other product produced in this reaction condition was excluded.[6]

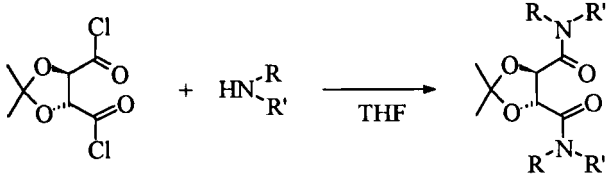
Scheme 1



1 2 3 4

Various 2,3-*O*-isopropylidene-L-tartaramides **5** could be easily prepared by aminolysis of the reactive L-tartaryl chloride **4** with primary and secondary amines. With excess amines quantitative amount of diamides **5** was prepared, and analytically pure products were obtained after column chromatography (Scheme 2). ^{1}H and ^{13}C NMR could distinguish the heterotopic dialkyl groups on the nitrogen atom in the chiral L-tartaramides **5**.

Scheme 2



4

5a R = H, R' = benzyl (91%)
5b R, R' = isopropyl (93%)
5c R, R' = isobutyl (89%)
5d R, R' = cyclohexyl (90%)

2,3-*O*-Isopropylidene- L-tartaramides **5** have a potential as ionophores for ion-selective electrodes. Numerous synthetic diamides have been known to display high selectivity to alkali metal ions and alkaline earth metal ions by strong dipole-pole complexation between dipolar amide groups and metal ion.[7]

These chiral L-tartaramides **5** also have a potential application as chiral auxiliaries and ligands specially in asymmetric synthesis. The unprotected diol of **5**, *N,N,N',N'*-tetramethyl-L-tartaramide has been used as enantiomerically pure chiral auxiliaries for chiral Lewis acids.[8] The chiral diamines reduced from L-tartaramides **5** also can be applied as chiral ligands for asymmetric dihydroxylation.[9]

EXPERIMENTAL

Synthesis of 2,3-*O*-isopropylidene-L-tartaryl chloride 4; was done from dimethyl tartrate ester **1** with three reaction steps without purification and characterization of synthetic intermediates: (a) Preparation of lithium 2,3-*O*-isopropylidene-L-tartrate **2**: Dimethyl 2,3-*O*-isopropylidene-L-tartrate **1** (4.4 g, 20 mmol) was treated with $LiOH \cdot H_2O$ (2.0 g) in methanol (45 mL) at room temperature for 2 days. The Li salt was used for next step after complete dryness under high vacuum. (b) Preparation of bis(trimethylsilyl) 2,3-*O*-isopropylidene-L-tartrate **3**: To the suspension of the dried lithium salt **2** (4.0 g) in THF (30 mL) containing 18-crown-6 (20 mg) under nitrogen, was added trimethylsilyl chloride (6.5 g, 60 mmol). The mixture after stirred for 3 hours became a clear solution. After solvent and excess TMSCl were removed *in vacuo*, and the trimethylsilyl L-

tartrate **3** with some inorganic residue was dried under high vacuum at room temperature. (c) Synthesis of L-tartaryl chloride **4**: To trimethylsilyl L-tartrate **3**, prepared above, in THF (30 mL) were added catalytic amount of DMF (two drops) and then oxalyl chloride (7.6 g) dropwise. After ceased gas evolution, the mixture was further stirred for 30 min. After removing the solvent and volatile excess reagent, the product, L-tartaryl chloride **4** (4.3 g, 94% from dimethyl tartrate ester **1**) was distilled under vacuum (51-55°C, 2 mmHg): mp 42-44 °C (icy solid); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.19 (s, 2H), and 1.54 (s, 6H); ^{13}CNMR ($CDCl_3$, 75 MHz) δ 172.0, 117.3, 83.6, and 26.8; IR (neat) 2995 w, 2964 w, 1799 s, 1740 s, 1229 m, 1123 m, 1008 m, 833 s cm^{-1}; Anal. Calcd for $C_7H_8O_4Cl_2$: C, 37.03; H, 3.55. Found: C, 36.74; H, 3.42.

General procedure for synthesis of L-Tartaramides by aminolysis of L-tartaryl chloride 4 with amines: To a solution of L-tartaryl chloride **4** (1.14 g, 5 mmol) in THF (20 mL) in an ice bath was added amine (15 mmol) dropwise. The mixture was stirred for one hour, and then the solid amine salt was filtered off. The filtrate was concentrated and dried *in vacuo*. The spectroscopically pure diamide product was obtained. The product could be further purified by chromatography on silica gel. Selected spectral data for **5a**: yield 1.67 g (91 %); mp 83-84 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (m, 10H), 4.63 (s, 2H), 4.50 (d, J = 5.7Hz, 4H), 1.46 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.5, 137.6, 128.7, 127.7, 127.6, 77.4, 43.3, 26.1; IR (KBr) 1685 and 1652 cm^{-1}; mass spectrum, *m/z* (rel intensity) 368 M^+ (23), 234 (7), 176 (100), 106 (75), 91 (77); Anal. Calcd for

$C_{21}H_{24}N_2O_4$: C, 68.48; H, 6.52; N, 7.50. Found: C, 68.30; H, 6.54; N, 7.50. for **5b**: yield 1.66 g (93 %); mp 123-124 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.44 (s, 2H), 4.44 (septet, J = 6.7 Hz, 2H), 3.42 (septet, J = 6.7 Hz, 2H), 1.40 (d, J = 6.7 Hz, 6H), 1.39 (d, J = 6.7 Hz, 6H), 1.38 (s, 6H), 1.20 (d, J = 6.7 Hz, 6H), 1.18 (d, J = 6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.1, 111.3, 76.3, 48.6, 46.0, 26.9, 20.7, 20.5 (double intensity by overlap), 20.5, 19.7; IR (KBr) 1636 cm^{-1}; mass spectrum, *m/z* (rel intensity) 356 M^+ (1.9), 170 (55), 100 (46), 46 (100); Anal. Calcd for $C_{19}H_{36}N_2O_4$: C, 64.01; H, 10.18; N, 7.86. Found: C, 63.98 ; H, 10.22 ; N,7.66. for **5c**: yield 1.83 g (89 %, colorless oil); ^{1}H NMR ($CDCl_3$, 300MHz) δ 5.31 (s, 2H), 3.40 (dd, J = 14.7 and 8.7 Hz, 2H), 3.37 (dd, J = 13.2 and 7.5 Hz, 2H), 3.25 (dd, J = 14.7 and 6.9 Hz, 2H), 3.07 (dd, J = 13.2 and 7.5 Hz, 2H), 2.00 (m, 4H), 1.45 (s, 6H), 0.937 (d, J = 6.3 Hz, 6H), 0.922 (d, J = 6.9 Hz, 6H), 0.864 (d, J = 6.3 Hz, 6H), 0.860 (d, J = 6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.1, 111.9, 75.6, 54.6, 52.9, 27.7, 26.5, 26.2, 20.12, 20.07, 20.01, 19.96; IR (neat) 1731 and 1649 cm^{-1}; mass spectrum, *m/z* (rel intensity) 412 M^+ (10.2), 198 (100), 156 (25), 128 (84), 57 (21); Anal. Calcd for $C_{23}H_{44}N_2O_4$: C, 66.95; H, 10.75; N, 6.79. Found: C, 66.72 ; H, 10.79 ; N,6.90. for **5d**: yield 2.32 g (90%); mp 148-149 °C; ^{1}H NMR ($CDCl_3$, 300MHz) δ 5.42 (s, 2H), 3.91 (br t, 2H), 2.94 (br t, 2H), 2.46 (br m, 4H), 1.80 - 1.05 (m, 36H), 1.37 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.7, 111.4, 76.6, 57.4, 56.3, 31.2, 31.0, 30.0, 29.1, 27.0, 26.60, 26.56, 25.76, 25.61, 25.42, 25.38; IR (KBr) 1646 cm^{-1}; mass spectrum, *m/z* (rel intensity) 516 M^+ (6.2), 208 (7), 180 (100), 83 (86); Anal. Calcd for $C_{31}H_{52}N_2O_4$: C, 72.05; H, 10.14; N, 5.42. Found: C, 72.03 ; H, 10.19 ; N, 5.20.

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5. To characterize bis(trimethylsilyl) 2,3-*O*-isopropylidene-L-tartrate **3**, when the dried oily product **3** was subject to distill under high vacuum at elevated temperature, it become sponge-like solid material. However, when this solid material under nitrogen was treated as above with oxalyl chloride, L-tartaryl chloride **4** was obtained.
6. The IR spectrum of 2,3-*O*-isopropylidene-L-tartaryl chloride **4** was varied in significant when measuring in neat. When the absorption peaks at 1799 and 1740 cm^{-1} was disappearing, and the new peaks at 1808 and 1721 cm^{-1} was appearing. Apparently, The acid dichloride **4** was partially hydrolyzed and turns

to acid anhydride, 2,3-*O*-isopropylidene-L-tartaric anhydride; IR (neat) 2993 w, 2963 m, 1808 s, 1721 vs, 1260 s, 1226 m, 1091 s, 1017 s, 800 s cm^{-1}.

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