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Synthesis of chiral α-amino acids

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Abstract—A novel method for the synthesis of chiral α-amino acids has been developed where the acid functionality was constructed by oxidizing a hydroxymethyl group introduced by Evans' method in the α-position of an appropriate acid substrate and the amino part came from the amide of the original carboxyl group following a modified Hofmann rearrangement reaction.

While there are many forms of amino acids, all of the important amino acids found in living organisms are α-amino acids. In addition to the 20 natural ones, there are many other α-amino acids found in various natural products.[1] Total syntheses of these natural products depend largely on the efficient construction of these unusual α-amino acids. Although a large number of methods are available for the synthesis of α-amino acids,[2] there is always scope for the development of new and more efficient methods that could be useful for the synthesis of many of these unusual α-amino acids, en route to the total synthesis of their parent natural products. While our earlier method for the diastereoselective Strecker synthesis of α-amino acids using α-phenylglycinol as chiral auxiliary worked well for α-aryl substrates, the selectivities were not good with α-alkyl-substituted compounds.[3] In this paper, we describe a new method for the stereoselective synthesis of α-amino acids that works equally well with both alkyl and aryl-substituted compounds and can be applied to prepare both D- and L-isomers.

Scheme 1 outlines the steps involved in this novel method of synthesizing α-amino acids. The salient features of this route are: (a) the carboxyl group of the final amino acids was obtained by oxidation of an α-hydroxymethyl group that was introduced in the α-position of the corresponding carboxylic substrate by Evans' method;[4] (b) the original carboxyl group was converted to an amide that was transformed into the amino group by a modified Hofmann rearrangement reaction.[5]

The synthesis started with the chiral oxazolidinone **1**. Treatment of **1** with $TiCl_4$ in the presence of diisopropylethylamine (DIPEA) in CH_2Cl_2 provided the Ti-enolate that was reacted with benzyloxymethyl chloride following Evans' method[4] to furnish the Bn-protected α-hydroxymethyl-substituted intermediate **2**[6] with excellent diastereoselectivity (>98%).[7] Removal of the chiral auxiliary[8] using $LiOH–H_2O_2$ led to the formation of an acid **3**[6] that was transformed into its amide **4** in the next step by the mixed anhydride method.[9] Treatment of **3** with ethyl chloroformate in the presence of Et_3N gave an intermediate mixed anhydride which was reacted in situ with NH_4OH to provide the amide **4**. With the amide in hand, the stage was now set to carry out the crucial Hofmann rearrangement reaction.[5] Accordingly, the amide **4** was treated with [bis(trifluoroacetoxy)iodo]benzene [$PhI(CF_3COO)_2$] in $CH_3CN–H_2O$ (1:1) to provide the corresponding amine that was treated in situ with Boc_2O and Et_3N to furnish the Boc-protected intermediate **5**. The Bn-protection was removed by hydrogenation over $Pd(OH)_2–C$ and the resulting primary hydroxyl of **6** was oxidized to the acid using $RuCl_3–NaIO_4$ furnishing the *N*-Boc protected α-amino acids **7** in excellent overall yields. Finally, treatment with dilute HCl removed the Boc-protection to give, after evaporation to dryness under reduced pressure, the desired D-amino acid **8** as its HCl salt.[6]

Compound **7a** on treatment with CH_2N_2 in ether gave Boc-D-Ala-OMe that showed rotation, $[\alpha]_D^{22} = +45.2$ (*c* 1.75, MeOH), matching with that of commercially available Boc-D-Ala-OMe.[10]

In conclusion, an excellent method for the synthesis of α-amino acids has been developed that will find useful applications in preparing many unusual α-amino acids

Keywords: α-amino acids; Hofmann rearrangement; oxazolidinone; Evans' reaction.

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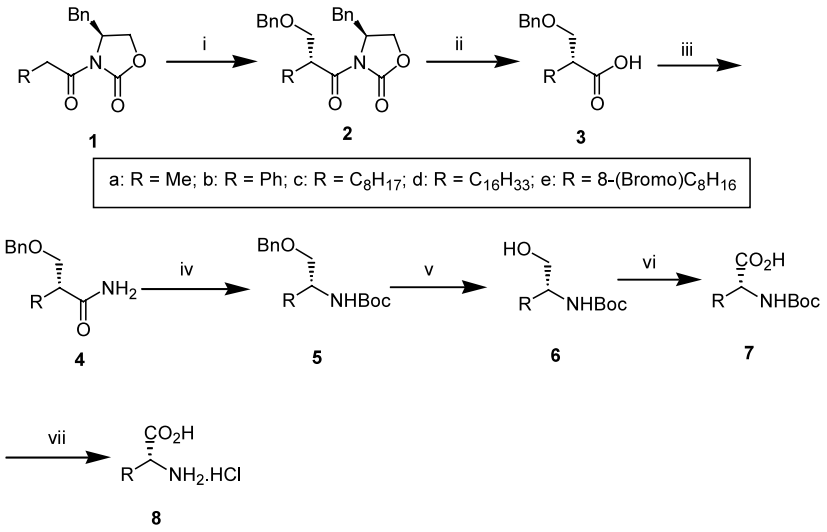

Scheme 1. Synthesis of α-amino acids. *Reagents and conditions*: (i) $TiCl_4$ (1.05 equiv.), DIPEA (1.1 equiv.), CH_2Cl_2, 0°C, 1 h, followed by $BnOCH_2Cl$ (2.0 equiv.), 0°C, 6 h (92% for **1a**, 87% for **1b**, 89% for **1c**, 80% for **1d** and 85% for **1e**). (ii) LiOH (2.0 equiv.), aq. H_2O_2 (30%, 6.0 equiv.), THF–H_2O (3:1, 0.05 M conc.), 0°C to rt, 5 h (87% for **2a**, 90% for **2b**, 91% for **2c**, 88% for **2d** and 86% for **2e**). (iii) Et_3N (1.1 equiv.), $ClCO_2Et$ (1.0 equiv.), THF, −20°C, 0.5 h, then NH_4OH (5.0 equiv.), 0°C, 1.5 h (90% for **3a**, 95% for **3b**, 92% for **3c**, 90% for **3d** and 93% for **3e**). (iv) $PhI(CF_3CO_2)_2$ (1.5 equiv.), CH_3CN–H_2O (1:1), rt, 2.5 h, then Boc_2O (2.0 equiv.), Et_3N (4.0 equiv.), 0°C, 1 h (72% for **4a**, 68% for **4b**, 73% for **4c**, 70% for **4d** and 66% for **4e**). (v) $Pd(OH)_2$–C (cat.), H_2, MeOH, rt, 1 h (95% for **5a**, 96% for **5b**, 93% for **5c**, 97% for **5d** and 90% for **5e**). (vi) $RuCl_3{\cdot}3H_2O$ (0.01 equiv.), $NaIO_4$ (3.0 equiv.), CCl_4–CH_3CN–H_2O (1:1:1.5), 0°C to rt, 1 h (75% for **6a**, 77% for **6b**, 68% for **6c**, 67% for **6d** and 62% for **6e**). (vii) dil. HCl, 0°C to rt, 1 h (95% for **7a**).

in either enantiomeric form starting from an appropriate chiral oxazolidinone. While L-phenylalanine-based oxazolidone **1** gives D-amino acids, as shown in this paper, its D-isomer could be similarly used to prepare the corresponding L-amino acids. Further work is in progress.

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10. Selected physical data for **7a** methyl ester: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.95 (s, 1H, BocN*H*), 4.28 (m, 1H, Cα*H*), 3.75 (s, 3H, CO_2Me), 1.40 (s, 9H, Boc), 1.36 (d, $J=6.9$ Hz, 3H, Me). $[\alpha]_D^{22}=+45.2$ (*c* 1.75, MeOH), matching with that of an authentic sample prepared from D-Ala. Selected physical data for **7b** methyl ester: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.30 (m, 5H, Ph), 5.50 (d, $J=6.6$ Hz, 1H, BocN*H*), 5.25 (d, $J=6.6$ Hz, 1H, Cα*H*), 3.70 (s, 3H, CO_2Me), 1.35 (s, 9H, Boc). $[\alpha]_D^{22}=-138.6$ (*c* 1.6, $CHCl_3$), matching with that of an authentic sample prepared from D-Phg. MS (LSIMS): *m*/*z* 210 (M^++Na–PhH), 166 (M^++H–$C_5H_8O_2$). Selected physical data for **7c** methyl ester: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.90 (d, $J=6.97$ Hz, 1H, BocN*H*), 4.25 (m, 1H, Cα*H*), 3.70 (s, 3H, CO_2Me), 1.20–1.80 (m, 14H, CH_2), 1.40 (s, 9H, Boc), 0.90 (t, $J=5.6$ Hz, 3H, Me). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 173.50, 155.50, 79.50, 53.41, 52.09, 32.70, 31.76, 29.28, 29.11, 28.26, 25.21, 22.58, 14.02. $[\alpha]_D^{22}=-13.8$ (*c* 1.85, $CHCl_3$). MS (LSIMS): *m*/*z* 302 (M^++H), 202 (M^++H–$C_5H_8O_2$). Selected physical data for **7d** methyl ester: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.95 (d, $J=7.90$ Hz, 1H, BocN*H*), 4.25 (m, 1H, Cα*H*), 3.75 (s, 3H, CO_2Me), 1.20–1.85 (m, 39H, CH_2 and Boc), 0.95 (t, $J=5.58$ Hz, 3H, Me). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 173.50, 155.33, 79.73, 53.41, 52.10, 32.71, 31.86, 29.51, 29.45, 29.33, 29.26, 29.14, 28.27, 27.96, 25.23, 22.63, 14.06. $[\alpha]_D^{22}=-11.51$ (*c* 2.5, $CHCl_3$). MS (LSIMS): *m*/*z* 355 (M^++H–CO_2CH_3). Selected physical data for **7e** methyl ester: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.95 (d, $J=6.54$ Hz, 1H, BocN*H*), 4.21 (m, 1H, Cα*H*), 3.70 (s, 3H, CO_2Me), 3.32 (t, $J=7.27$ Hz, 2H, CH_2Br), 1.10–1.90 (m, 14H, CH_2), 1.40 (s, 9H, Boc). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 173.44, 155.30, 79.74, 53.35, 52.12, 33.93, 32.72, 32.67, 29.19, 29.04, 28.62, 28.25, 28.05, 25.17. $[\alpha]_D^{22}=-10.42$ (*c* 2.0, $CHCl_3$). MS (LSIMS): *m*/*z* 279, 281 (M^+–$C_5H_8O_2$).