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One-Pot Synthesis of Chiral *N*-Protected-4-amino Functionalized But-2-enoates from α-Amino Acids Mediated by 1-Hydroxybenzotriazole

Giorgos Athanasellis, Efstathios Gavrielatos, and Olga Igglessi-Markopoulou*

Laboratory of Organic Chemistry, Department of Chemical Engineering, National Technical University of Athens, Zografou Campus, 15773 Athens, Greece

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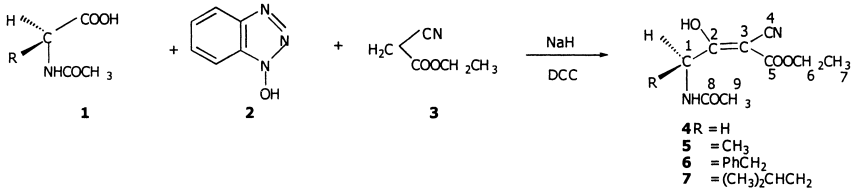
A novel one-pot synthetic route to 4-acetylamino-2-cyano-3-hydroxybut-2-enoates in good yields (63–71%) is reported. An HPLC analysis of these compounds showed very good enantiomeric excesses (90–94%), justifying the success of our methodology to maintain the stereochemical integrity of the starting materials used.

3-Hydroxy-4-amino acids, homologues of statine, are achieving increased pharmacological significance due to their participation in the bioactivity of peptides and their ability to act as selective renin inhibitors.[1–3] Especially, the functionalized enols of type I (Fig. 1) have been reported to possess topographical similarities with Boc-statine; therefore, they can be effective as inhibitors of HIV-1 protease.[4,5]

In continuation of our studies on the use of "active esters" of *N*-substituted α-amino acids as precursors for the synthesis of optically active tetramic acids and other heterocyclic compounds,[6–8] we developed a new 'one-pot' method for the synthesis of optically active 3-substituted tetramic acids using *N*-hydroxybenzotriazole esters of α-amino acids as chiral precursors.[9] During our attempts to expand this methodology by using a variety of C-acylation reagents, we recently managed to synthesize a series of 4-amino-2-cyano-3-hydroxybut-2-enoates **4**–**7** (Scheme 1) in good yields and very good enantiomeric ratios (better than previously reported[10]) (Table 1). The high optical purities of these compounds confirm that neither the *N*-hydroxybenzotriazole esterification nor the C-acylation reaction cause detectable racemization. Moreover, the synthesized butenoates **4**–**7** could serve as precursors of the statine family series (Fig. 1) under asymmetric hydrogenation conditions.[11]

Fig. 1. Compounds of the statine family series.

The proposed synthesis comprises a C-acylation reaction between an active methylene compound and the *N*-hydroxybenzotriazole ester of the appropriate optically active amino acid. The *N*-hydroxybenzotriazole ester was synthesized by treatment of the appropriate optically active *N*-acetyl α-amino acid **1** (10 mmol) with 1-hydroxybenzotriazole (10 mmol) and DCC (10 mmol) in anhydrous THF (40 mL) at 0 °C. The reaction mixture was filtered off and the filtrate was added into a thick slurry mixture containing the sodium salt of the active methylene compound [prepared from the addition of NaH (20 mmol) in anhydrous THF (80 mL) and ethyl cyanoacetate (10 mmol)]. After stirring for 2.5 h, the solvent was removed under reduced pressure. The residue was diluted with water, and washed with diethyl ether, and the aqueous layer was acidified with 10% HCl to give products **4**–**7** as white solids. One first remark concerning our methodology is that the molar ratio between the amino acid **1** and ethyl cyanoacetate **3** does not affect the product of the reaction, in contrast to what was previously reported.[9] Thus, when ethyl cyanoacetate **3** was used in stoichiometric ratio (1:1) or in molar excess (2:1) to the *N*-acetyl α-amino acid **1**, compounds **4**–**7** were obtained, and not the corresponding cyclized compounds. In addition, the treatment of compounds **4**–**7** under basic conditions (EtONa/EtOH, rt) did not afford the corresponding cyclized compounds. Nevertheless, these compounds can be afforded by the treatment of compounds **4**–**7** with 10% HCl in MeOH.[10] The merits of the proposed synthetic route in contrast to the previously described methodology[10] are as follows. Because there is no need for isolating the intermediates *N*-hydroxybenzotriazole esters of the chiral α-amino acids, the products are obtained in a one-step reaction. This fact reduces the time for synthesizing the desired products, and is beneficial for the overall yield of the reaction (63–71%). Moreover, an HPLC analysis of optically active products **5**–**7** indicates the success of the proposed methodology to maintain the stereochemical integrity of the corresponding α-amino acids. The reaction is simple, inexpensive, easily scaled-up and proceeds with low racemization. Finaly, in contrast to the *N*-hydroxysuccinimide esters of α-amino acids, the use of *N*-hydroxybenzotriazole esters as



Scheme 1. Synthesis of compounds **4**–**7**.

Table 1. Optical Rotations, Retention Times and Enantiomeric Excesses of Compounds **4**–**7**

Compound	Yield/%[b)]	$[\alpha]_D$[a)] (*c* 1, MeOH)	Retention time/min	Enantiomeric excess[b)]
4	63	—	—	—
5	68 (50)	+18.2	5.58:6.07	94 (68)
6	68 (45)	+88.3	5.12:6.82	90 (56)
7	71 (65)	+ 3.2	5.42:6.13	92 (84)

a) Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. Enantiomeric ratios were determined by HPLC analysis with a CHIRALPAK AS column (4.6 × 250 mm), [254 nm, 0.6 mL/min, ethanol-hexane (1:1). b) Numbers in brackets refer to the results of the previously described methodology.[9b]

building blocks in the C-acylation reaction would also open the possibility of using bases strong enough to abstract a proton from different types of carbonyl systems with a functional α-CH group acting not only as an electron-withdrawing group (CN), but also as an electron donor. The structures of compounds **4**–**7** have been elucidated by elemental analyses as well as NMR and FT-IR Spectroscopy.[12]

In conclusion, we successfully synthesized *N*-protected 4-amino functionalized but-2-enoates **4**–**7** in very good enantiomeric ratios by using a series of chiral *N*-acetyl α-amino acids and 1-hydroxybenzotriazole, a useful precursor in the synthesis of peptides. Work currently in progress includes applications of the proposed methodology in the synthesis of functionalized 4-amino-3-hydroxy- and 3,4-dihydroxybut-2-enoates as well as their cyclization reactions to tetramic and tetronic acids,[13] respectively. Additionaly, the catalytic asymmetric hydrogenation of the above-reported functionalized 4-hydroxybut-2-enoates to "statine-homologues" is under investigation.

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12 Typical analytical and spectroscopic data: ^{1}H/^{13}C-NMR spectra (*J* in Hz; 300 and 75 MHz) were measured in $CDCl_3$. **4**: 71% yield; mp 126–127 °C; IR (KBr) 3300 (NH), 2223 (CN), 1656/1581 (CO), and 1544 cm^{-1} (C=C) ; ^{1}H NMR δ 1.37 (3H, t, J = 7.5, CH_3), 2.08 (3H, s, $COCH_3$), 4.36 (4H, m, $COOCH_2CH_3$ and $CH_2NHCOCH_3$), 5.99 (1H, s, NH); ^{13}C NMR δ 13.9 (C-7), 22.6 (C-9), 41.6 (C-1), 62.9 (C-6), 80.2 (C-3), 113.6 (C-4), 170.2 (C-5), 170.7 (C-8), 185.9 (C-2); Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.66; N, 13.21%; Found: C, 50.77; H, 5.43; N, 13.43%. **5**: 63% yield; mp 111–112 °C; IR (KBr) 3286 (NH), 2221 (CN), 1649/1588 (CO), and 1553 cm^{-1}(C=C) ; ^{1}H NMR δ 1.36 (3H, t, CH_2CH_3), 1.48 (3H, d, J = 6.9, CH_3), 2.03 (3H, s, $COCH_3$), 4.34 (2H, q, J = 6.9, CH_2CH_3), 4.91 (1H, q, CH_3CH), 5.90 (1H, s, NH); ^{13}C NMR δ 13.9 (C-7), 18.2 (CH_3), 22.6 (C-9), 48.3 (C-1), 62.9 (C-6), 79.3 (C-3), 113.6 (C-4), 170.0 (C-5), 170.5 (C-8), 190.0 (C-2); Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.10; H, 6.19; N, 12.39%; Found: C, 53.11; H, 6.22; N, 12.47%. **6**: 68% yield; mp 146–147 °C; IR (KBr) 3304 (NH), 2223 (CN), 1654/1592 (CO), and 1540 cm^{-1} (C=C) ; ^{1}H NMR δ 1.35 (3H, t, $COOCH_2CH_3$), 1.99 (3H, s, $COCH_3$), 3.05 (1H, dd, J = 6.9, CH_2), 3.14 (1H, dd, J = 6.9, CH_2), 4.33 (2H, q, J = 6.9, CH_2CH_3), 5.14 (1H, q, J = 6.9, CH), 5.81 (1H, d, J = 6.9, NH), 7.20–7.37 (5H, m, PhH); ^{13}C NMR δ 13.9 (C-7), 22.6 (C-9), 38.3 ($PhCH_2$), 53.5 (C-1), 62.9 (C-6), 80.6 (C-3), 113.5 (C-4), 134.8/129.1/129.0/127.7 (phenyl carbons), 170.0 (C-5), 170.4 (C-8), 188.2 (C-2); Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.58; H, 5.96; N, 9.27%; Found: C, 63.47; H, 5.78; N, 9.41. 7: 67% yield; mp 96–97 °C; IR (KBr) 3318 (NH), 2221 (CN), 1656/1582 (CO), and 1546 cm^{-1} (C=C) ; ^{1}H NMR δ 0.98 (3H, d, J = 6.9, CH_3), 0.99 (3H, d, J = 6.9, CH_3), 1.36 (3H, t, $COOCH_2CH_3$), 1.60–1.69 (3H, m, $(CH_3)_2CHCH_2$), 2.04 (3H, s, $COCH_3$), 4.32 (2H, q, J = 6.9, $COOCH_2CH_3$), 4.89 (1H, q, J = 6.9, CH), 5.83 (1H, d, J = 7.2, NH), 13.9 (1H, br s, OH); ^{13}C-NMR δ 13.9 (C-7), 21.5 ($(CH_3)_2CHCH_2$), 22.7 (C-9), 22.8 ($(CH_3)_2CHCH_2$), 24.8 ($(CH_3)_2CHCH_2$), 41.5 ($(CH_3)_2CHCH_2$), 51.1 (C-1), 62.8 (C-6), 79.7 (C-3), 113.8 (C-4), 170.1 (C-5), 170.5 (C-8), 190.0 (C-4); Anal. Calcd. for $C_{13}H_{20}N_2O_4$: C, 58.21, H, 7.46; N, 10.45%; Found: C, 57.99; H, 7.47; N, 10.37%.

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