Synthesis of 4,5-Dihydro-1*H*-imidazole-4-carboxylates from α-Amino Acid Amidines

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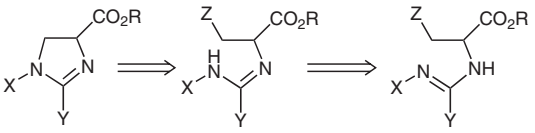
Abstract: Various β-hydroxy-substituted amidines were obtained starting from methyl serinates, aldehydes or ketones, and tosyl azide. These were converted via Mitsunobu intramolecular cyclization into enantiomerically pure methyl 2-alkyl-1-tosyl-4,5-dihydro-1*H*-imidazole-4-carboxylates.

Key words: *N*,*N*′-disubstituted amidines, intramolecular cyclization, Mitsunobu reaction, 4,5-dihydro-1*H*-imidazole-4-carboxylates, amino acid

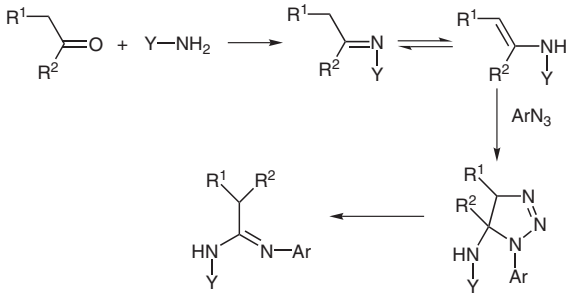
4,5-Dihydro-1*H*-imidazole derivatives and particularly 4,5-dihydro-1*H*-imidazole-4-carboxylic acids have attracted substantial interest due to their interesting biological activity.[1] In addition, these heterocycles have useful functions, e.g. as chiral auxiliaries,[2] chiral catalysts,[3] and ligands for asymmetric catalysis.[4] Furthermore there are very few reports of the synthesis of imidazole-based amino acids.[5] The aim of this work was the synthesis of 4,5-dihydro-1*H*-imidazole-4-carboxylic acid derivatives from α-amino acid ester amidines following the retrosynthetic route shown in Scheme 1.



Scheme 1

Our group recently reported a simple and useful synthetic entry to optically pure α-amino acid amidines through heterocyclic transformations.[6] The cycloaddition of tosyl azide with enamines gives 4,5-dihydrotriazole intermediates, which, by loss of nitrogen and transposition of the R^2 substituent from position 5 to 4, are transformed into the expected amidines (Scheme 2). Starting from amino acid esters, carbonyl compounds, and tosyl azide, we obtained directly the amidines containing the entire amino acid function.

With the aim to realize the proposed retrosynthetic scheme and to synthesize β-substituted amidines, methyl serinates were selected as the amino acid substrate. To avoid unwelcome secondary reactions, the serine hydroxy



Scheme 2

group was protected as the trimethylsilyl ether. The protected L-serine methyl ester (*S*)-**1** was reacted with cyclohexanone (**2a**) and tosyl azide yielding amidine (*S*)-**3a**. Finally the silyl group was removed by acid hydrolysis with citric acid[7] and the amidine (*S*)-**4a** with a free hydroxy group was easily obtained. The structure of (*S*)-**3a** and (*S*)-**4a** was established by analytical and spectroscopic data. Due to the good results, the reaction was extended to butanal (**2b**) and phenylacetaldehyde (**2c**) (Scheme 3, Table 1). Cyclohexanone (**2a**) was also reacted with D-serine (*R*)-**1**.

Table 1 β-Hydroxy-Substituted Amidines **4**

Substrates	Product(s)	R^1	R^2	Yield (%)
(*S*)-**1** + **2a**	(*S*)-**4a**	$(CH_2)_4$		56
(*R*)-**1** + **2a**	(*R*)-**4a**	$(CH_2)_4$		62
(*S*)-**1** + **2b**	**4b**	Et	H	51
(*S*)-**1** + **2c**	**4c** + **4d**	Ph	H	31 + 23

As expected, the behavior of phenylacetaldehyde (**2c**), was different from that of the other carbonyl compounds.[8] In the literature examples, phenylacetaldehyde can react with ketones or aldehydes and tosyl azide to give formamidines with loss of diazophenylmethane. In this case a substantial amount of phenylacetamidine **3c** was obtained beside the expected formamidine **3d**. All protected amidines were hydrolyzed and to give **4a**–**d** with a free hydroxy group. It is of interest to note that the amidines **3** and **4**, arising from optically pure amino acids, retain their optical activity. The intramolecular cyclization of the amidines **4a**–**c**, target of this study, was easily performed under Mitsunobu conditions. The reaction was carried out

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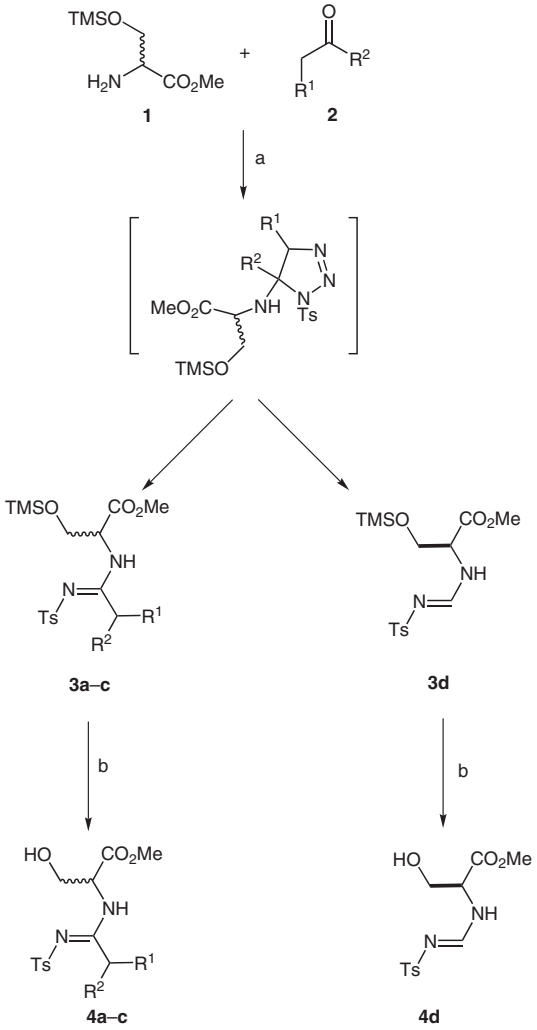
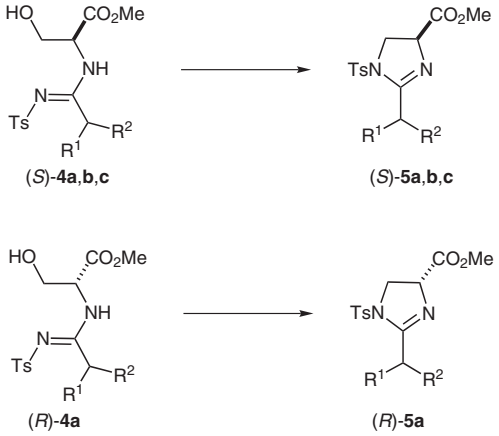


Scheme 3 *Reagents and conditions*: (a) amino acid ester **1** (6 mmol), carbonyl compound **2** (6 mmol), TsN_3 (6 mmol), MS 4 Å (7 g), CH_2Cl_2, r.t., 16–18 h; (b) citric acid (6 mmol), MeOH, r.t., 2 h.

under an inert atmosphere with anhydrous tetrahydrofuran as solvent. A molar amount of diethyl azodicarboxylate and triphenylphosphine was added to the solution of amidine **4a–c** (Scheme 4, Table 2). The cyclization reaction was accomplished in 1–2 hours affording methyl 2-alkyl-1-tosyl-4,5-dihydro-1*H*-imidazole-4-carboxylates **5a–c**. The ^{1}H NMR, ^{13}C NMR spectra, and mass data were in agreement with the proposed structures. Cyclization of **4d** gave several indistinct products.

The separation of the reaction byproducts from products **5** was difficult and time consuming. In fact the crude reaction mixtures were evaporated and diethyl hydrazine-1,2-dicarboxylate was partially removed by crystallizing twice from toluene (other dialkyl azodicarboxylates showed a similar solubility). After evaporation the crude residue was chromatographed on a silica gel column. Some fractions had to be discarded as they were contaminated by diethyl hydrazine-1,2-dicarboxylate. Diethyl azodicarboxylate polymer-supported[9] and polyfluorinated reagents[10] were tested without encouraging results.



Scheme 4 *Reagents and conditions*: amidine (1 mmol), Ph_3P (1 mmol), DEAD (1 mmol), THF, r.t., 2 h.

Table 2 Methyl 2-Alkyl-1-tosyl-4,5-dihydro-1*H*-imidazole-4-carboxylates **5a–c**

Substrate	Product	R^1	R^2	Yield (%)
(*S*)-**4a**	(*S*)-**5a**	$(CH_2)_4$		45
(*R*)-**4a**	(*R*)-**5a**	$(CH_2)_4$		47
4b	**5b**	Et	H	39
4c	**5c**	Ph	H	32

Products **5a–c**, examined by HPLC using chiral column (Chiralcell OD, hexane–*i*-PrOH, 7:3 as eluent), showed the retention of the original enantiomeric purity.

Mps were determined by a Büchi 510 (capillary) apparatus. Optical rotation was measured with Perkin Elmer 343 Plus polarimeter (*c* 10% in $CHCl_3$; 20 °C). IR spectra were measured with a JASCO IR Report 100 instrument. NMR spectra were obtained with Bruker Advance 300 and Varian Gemini 200 instruments. *J* values are given in Hz for solutions in $CDCl_3$. HPLC was performed with HP 1050 DAD, Merck–Hitachi L 7100 pump, Rheodyne loop 20 µL injector, Chiralcel OD column, 1 mL/min flow. MS were recorded with LCQ Advantage Thermofinnigan equipped with electrospray ionization. (*S*)- or (*R*)-*O*-(Trimethylsilyl)serine was synthesized by a literature method[11] from (*S*)- or (*R*)-serine methyl ester hydrochloride.

Amidines 4a–d: General Procedure

(*S*)- or (*R*)-*O*-(Trimethylsilyl)serine **1** (6 mmol) was suspended in CH_2Cl_2 (20 mL) and carbonyl compound **2a–c** (6 mmol), molecular sieves 4 Å (7 g), and tosyl azide (6 mmol) were added. The mixture was stirred at r.t. until disappearance of starting material (TLC, EtOAc–cyclohexane, 1:1; 16–18 h). The suspension was filtered and evaporated. The crude product **3** was suspended in MeOH (10 mL) and citric acid (6 mmol) was added. The mixture was stirred at r.t. for 2 h and then evaporated. The resulting raw amidine **4** was washed with $NaHCO_3$ soln, dried (Na_2SO_4), and purified by chromatography (silica gel, EtOAc–cyclohexane, 1:1).

Methyl (*S*)-2-{[Cyclopentyl(tosylimino)methyl]amino}-3-hydroxypropanoate [(*S*)-4a]

White crystals (EtO_2–pentane); yield: 56%; mp 84 °C.

$[\alpha]_D^{20}$ +21.34 (*c* 10% in $CHCl_3$).

IR (Nujol): 1740 cm^{-1} (C=O).

^1H NMR (200 MHz): δ = 1.64–2.37 (m, 9 H, cyclopentyl, OH), 2.40 (s, 3 H, CH_3), 3.75 (s, 3 H, OCH_3), 3.80–3.91 (m, 1 H, CHC=N), 3.90–4.00 (m, 2 H, CH_2O), 4.58–4.65 (m, 1 H, CH=N), 6.45 (d, *J* = 6.6 Hz, 1 H, NH), 7.23–7.42 (m, 2 H, ArH), 7.75–7.86 (m, 2 H, ArH).

^{13}C NMR (75 MHz): δ = 21.7 (CH_3), 25.8 (CH_2), 25.8 (CH_2), 32.1 (CH_2), 32.2 (CH_2), 43.0 (CH), 56.4 (CH_3), 56.4 (CH), 62.1 (CH_2), 126.4 (CH), 129.4 (CH), 140.9 (C), 142.5 (C), 170.6 (C), 172.4 (C).

MS (ESI): *m*/*z* = 369.2 [M + H^+]

Anal. Calcd for $C_{17}H_{24}N_2O_5S$: C, 55.42; H, 6.57; N, 7.60. Found: C, 55.30; H, 6.77; N, 7.48.

Methyl (*R*)-2-{[Cyclopentyl(tosylimino)methyl]amino}-3-hydroxypropanoate [(*R*)-4a]

White crystals (EtO_2–pentane); yield: 62%; mp 84 °C.

$[\alpha]_D^{20}$ –21.34 (*c* 10% in $CHCl_3$).

Methyl (*S*)-3-Hydroxy-2-{[1-(tosylimino)butyl]amino}propanoate (4b)

Light yellow oil; yield: 51%.

$[\alpha]_D^{20}$ +21.82 (*c* 10% in $CHCl_3$).

IR (Nujol): 1744 cm^{-1} (C=O).

^1H NMR (200 MHz): δ = 0.99 (t, *J* = 8.10 Hz, 3 H, CH_3), 1.69–1.84 (m, 2 H, CH_2), 2.40 (s, 3 H, CH_3), 2.60 (br s, 1 H, OH), 2.70–2.93 (m, 2 H, CH_2), 3.64 (s, 3 H, CH_3), 3.91–3.94 (m, 2 H, CH_2O), 4.61–4.68 (m, 1 H, CH), 6.58 (d, *J* = 7.0 Hz, 1 H, NH), 7.26 (d, *J* = 7.1 Hz, 2 H, ArH), 7.76 (d, *J* = 7.1 Hz, 2 H, ArH).

^{13}C NMR (75 MHz): δ = 13.9 (CH_3), 20.9 (CH_2), 21.7 (CH_3), 35.8 (CH_2), 53.1 (CH_3), 56.6 (CH), 62.2 (CH_2), 126.6 (CH), 129.6 (CH), 140.6 (C), 142.6 (C), 169.0 (C), 170.5 (C).

MS (ESI): *m*/*z* = 343.3 [M + H^+].

Anal. Calcd for $C_{15}H_{22}N_2O_5S$: C, 52.62; H, 6.48; N, 8.18. Found: C, 52.48; H, 6.66; N, 8.01.

Methyl (*S*)-3-Hydroxy-2-{[2-phenyl-1-(tosylimino)ethyl]amino}propanoate (4c)

Light yellow oil; yield: 31%.

$[\alpha]_D^{20}$ +22.98 (*c* 10% in $CHCl_3$).

IR (Nujol): 1750 cm^{-1} (C=O).

^1H NMR (200 MHz): δ = 2.04 (br s, 1 H, OH), 2.40 (s, 3 H, CH_3), 3.67 (s, 3 H, OCH_3), 3.85–3.89 (m, 2 H, CH_2O), 4.31 (s, 2 H, CH_2Ph), 4.49–4.62 (m, 1 H, CH), 6.29 (d, *J* = 8.3 Hz, 1 H, NH), 7.21–7.38 (m, 7 H, ArH), 7.77 (d, *J* = 7.14 Hz, 2 H, ArH).

^{13}C NMR (75 MHz): δ = 21.7 (CH_3), 39.7 (CH_2), 53.1 (CH_3), 56.7 (CH), 62.0 (CH_2), 126.6 (CH), 128.4 (CH), 129.5 (CH), 129.6 (CH), 130.2 (CH), 132.9 (C), 140.3 (C), 142.8 (C), 166.9 (C), 170.1 (C).

MS (ESI): *m*/*z* = 391.3 [M + H^+].

Anal. Calcd for $C_{19}H_{22}N_2O_5S$: C, 58.45; H, 5.68; N, 7.17. Found: C, 58.36; H, 5.79; N, 6.96.

Methyl (*S*)-3-Hydroxy-2-{[(tosylimino)methyl]amino}propanoate (4d)

Light yellow oil; yield: 23%.

$[\alpha]_D^{20}$ +21.60 (*c* 10% in $CHCl_3$).

IR (Nujol): 1742 cm^{-1} (C=O).

^1H NMR (200 MHz): δ = 1.79 (br, 1 H, OH), 2.39 (s, 3 H, CH_3), 3.76 (s, 3 H, OCH_3), 3.80–4.10 (m, 2 H, CH_2), 4.68–4.75 (m, 1 H, CH), 6.93 (br s, 1 H, NH), 7.26 (d, *J* = 7.14 Hz, 2 H, ArH), 7.73 (d, *J* = 7.14 Hz, 2 H, ArH), 8.34 (d, *J* = 5.01 Hz, 1 H, CH=N).

^{13}C NMR (75 MHz): δ = 21.50 (CH_3), 53.3 (CH_3), 56.3 (CH), 61.8 (CH_2), 126.6 (CH), 129.4 (CH), 138.4 (C), 143.1 (C), 157.4 (C), 169.8 (C).

MS (ESI): *m*/*z* = 301.2 [M + H^+].

Anal. Calcd for $C_{12}H_{16}N_2O_5S$: C, 58.04; H, 7.14; N, 9.02. Found: C, 57.89; H, 7.30; N, 8.98.

Methyl 2-Alkyl-1-tosyl-4,5-dihydro-1*H*-imidazole-4-carboxylates 5a–c: General Procedure

The amidine **4a–c** (1 mmol) was dissolved in anhyd THF (10 mL) under N_2 at r.t. Ph_3P (1 mmol) and DEAD (1 mmol) were added and the mixture was stirred for 2 h until disappearance of starting materials (TLC, EtOAc–cyclohexane, 3:2). The soln was evaporated at reduced pressure and diethyl hydrazine-1,2-dicarboxylate was removed by repeated crystallization (toluene). The toluene soln was evaporated and the residue chromatographed (EtOAc–cyclohexane, 1:1).

Methyl (*S*)-2-Cyclopentyl-1-tosyl-4,5-dihydro-1*H*-imidazole-4-carboxylate [(*S*)-5a]

Light yellow oil; yield: 45%.

$[\alpha]_D^{20}$ +80.60 (*c* 10% in $CHCl_3$).

IR (Nujol): 1744 cm^{-1} (C=O).

^1H NMR (300 MHz): δ = 1.60–1.99 (m, 8 H, 4 CH_2), 2.40 (s, 3 H, CH_3), 3.29–3.40 (m, 1 H, CHC=N), 3.67 (s, 3 H, CH_3O), 3.91–4.09 (m, 2 H, CH_2), 4.51–4.60 (m, 1 H, CH), 7.31 (d, *J* = 7.14 Hz, 2 H, ArH), 7.76 (d, *J* = 7.14 Hz, 2 H, ArH).

^{13}C NMR (75 MHz): δ = 21.8 (CH_3), 25.8 (CH_2), 25.9 (CH_2), 32.1 (CH_2), 32.4 (CH_2), 38.9 (CH), 50.8 (CH_2), 52.8 (CH_3), 65.5 (CH), 127.4 (CH), 130.3 (CH), 135.6 (C), 144.9 (C), 166.2 (C), 171.3 (C).

MS (ESI): *m*/*z* = 351.3 [M + H^+].

Anal. Calcd for $C_{17}H_{22}N_2O_4S$: C, 58.27; H, 6.33; N, 7.99. Found: C, 58.02; H, 6.50; N, 7.78.

Methyl (*R*)-2-Cyclopentyl-1-tosyl-4,5-dihydro-1*H*-imidazole-4-carboxylate [(*R*)-5a]

Light yellow oil; yield: 47%.

$[\alpha]_D^{20}$ –80.60 (*c* 10% in $CHCl_3$).

Methyl (*S*)-2-Propyl-1-tosyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (5b)

Light yellow oil; yield: 39%.

$[\alpha]_D^{20}$ +79.4 (*c* 10% in $CHCl_3$).

IR (Nujol): 1740 cm^{-1} (C=O).

^1H NMR (200 MHz): δ = 0.99 (t, *J* = 7.95 Hz, 3 H, CH_3), 1.73–1.85 (m, 2 H, CH_2), 2.40 (s, 3 H, $C_6H_4CH_3$), 2.80–2.95 (m, 2 H, CH_2), 3.69 (s, 3 H, OCH_3), 4.05–4.25 (m, 2 H, CH_2), 4.74–4.83 (m, 1 H, CH), 7.39 (d, *J* = 7.14 Hz, 2 H, ArH), 7.77 (d, *J* = 7.14 Hz, 2 H, ArH).

^{13}C NMR (75 MHz): δ = 13.9 (CH_3), 19.1 (CH_2), 21.7 (CH_3), 38.3 (CH_2), 44.7 (CH_2), 52.4 (CH), 53.0 (CH_3), 127.2 (CH), 130.0 (CH), 136.9 (C), 143.9 (C), 170.9 (C), 173.9 (C).

MS (ESI): *m*/*z* = 325.2 [M + H^+].

Anal. Calcd $C_{15}H_{20}N_2O_4S$: C, 55.54; H, 6.21; N, 8.64. Found: C, 55.36; H, 6.35; N, 8.57.

Methyl (*S*)-2-Benzyl-1-tosyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (5c)

Light yellow oil; yield: 32%.

$[\alpha]_D^{20}$ +78.6 (*c* 10% in $CHCl_3$).

IR (Nujol): 1743 cm^{-1} (C=O).

^{1}H NMR (200 MHz): δ = 2.40 (s, 3 H, $C_6H_4CH_3$), 3.74 (s, 3 H, OCH_3), 4.00–4.13 (m, 2 H, CH_2), 4.21 (s, 2 H, CH_2Ph), 4.67–4.71 (m, 1 H, CH), 7.05–7.75 (m, 9 H, ArH).

^{13}C NMR (75 MHz): δ = 21.5 (CH_3), 35.4 (CH_2), 50.2 (CH_2), 52.7 (CH_3), 65.4 (CH), 127.0 (CH), 127.2 (CH), 128.5 (CH), 129.2 (CH), 128.9 (CH), 134.8 (C), 134.9 (C), 144.6 (C), 160.2 (C), 170.8 (C).

MS (ESI): *m*/*z* = 373.3 [M + H$^+$].

Anal. Calcd $C_{19}H_{20}N_2O_4S$: C, 61.27; H, 5.41; N, 7.52; Found: C, 61.05; H, 5.63; N, 7.43.

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