CONVENIENT AND STEREOSPECIFIC SYNTHESIS OF *trans*-1,3-DISUBSTITUTED IMIDAZOLIDINES AND THEIR TRANSFORMATION TO 2,3-DIAMINO-3-PHENYLPROPANOIC ACIDS+

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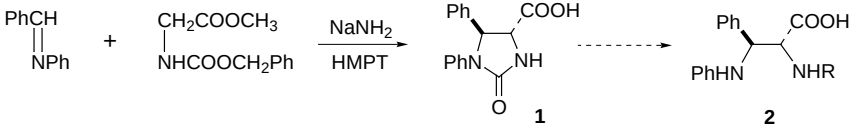
Conversion of the easily available *trans*-2-oxoimidazolidine-4-carboxylic acid **1** to the corresponding imidazolidines **8** gives after one-step oxidation and ring cleavage the diamino acid **2** in high yield. The difference in the *trans*-vicinal couplings for the hydrogen-bonded and nonbonded compounds suggests different ring geometry as a result of the balancing effect of the N^1 substituent on the "allylic strain".

Key words: Amino acids; 2,3-Diaminocarboxylic acids; Imidazolidines; Ring cleavage; Reductions; Steric interactions.

The synthesis of 2,3-diaminocarboxylic acids has attracted considerable interest due to the important role of these nonproteinogenic amino acids as constituents of several antibiotics such as bleomycin[1] and of other biologically active substances[2a]. Only few useful methods for the stereocontrolled synthesis of 2,3-diaminocarboxylic acids, mostly multi-step ones, have been reported[2].



SCHEME 1

We now report a new shorter approach, as outlined in Scheme 1, for the stereospecific synthesis of 2,3-diamino-3-phenylpropanoic acids, *via trans*-

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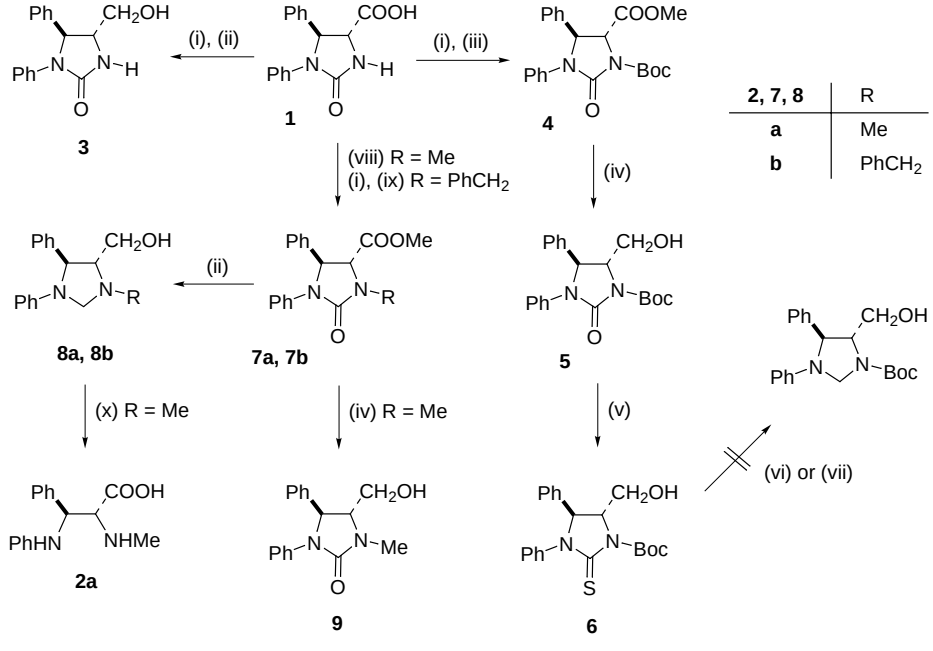
imidazolidines **8**, starting from *trans*-2-oxoimidazolidine-4-carboxylic acid **1**, recently obtained by us in a one-step procedure from easily available materials[3].

The ring deoxygenation of **1** seemed to be a means of obtaining an imidazolidine which could then lead under mild conditions to the desired 2,3-diaminopropanoic acid. Attempts to achieve deoxygenation of the cyclic urea fragment of the methyl ester of **1** by $LiAlH_4$ reduction were unsuccessful. Only compound **3** (Scheme 2) was isolated in an essentially quantitative yield using an excess of the reagent even after prolonged reflux, analogously to the incomplete reduction of some hydantoins to the corresponding 2-imidazolidinones[4]. Compound **1** was easily transformed to the *N*-protected ester **4**, which was reduced with $NaBH_4$ to give compound **5**. The thioxo compound **6** was prepared using Lawesson reagent. However, desulfurization at this compound under several conditions failed (Scheme 2). A two-step deoxygenation sequence was further employed. The $LiAlH_4$ reduction after the preliminary *N*-alkylation of the methyl ester of **1** was



(i) MeOH, BF_3-Et_2O; (ii) $LiAlH_4$, Et_2O; (iii) Boc_2O, DMAP, Et_3N, CH_2Cl_2; (iv) $NaBH_4$, MeOH; (v) Lawesson reagent, toluene, heating; (vi) Raney Ni, EtOH; (vii) $NaBH_4$, $CoCl_2$, EtOH; (viii) MeI, Ag_2O, DMF; (ix) $PhCH_2Br$, Ag_2O, DMF; (x) CrO_3, aqueous AcOH

SCHEME 2

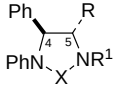
used. By performing the reaction at room temperature, complete reduction of the N^1 alkylated compounds **7a** and **7b** occurred quantitatively in a relatively short time, affording imidazolidines **8a** and **8b**, respectively. This finding could be explained by the increased solubility of the *N*,*N*-disubstituted compounds. This could be also the reason for the difference in $LiAlH_4$ reduction of *trans*-5,6-diphenyldihydrouracil[5] and its *N*-methyl derivative[7a]. As expected, compound **7a** can be reduced with $NaBH_4$ to compound **9**.

Oxidation at the hydroxymethyl group and the imidazolidine ring opening in compound **8a** proceeded in a one-step procedure using CrO_3 in aqueous acetic acid. Ion-exchange chromatography afforded the free amino acid **2a** in 75% yield as a *threo* racemate, still contaminated with small amounts of chromium. Our attempts to obtain compound **2b** from compound **8b** were not successful because of difficulties in the acid purification from $Cr(OH)_3$.

Since compound **1** had *trans*-configuration and all the transformations proceded with retention of configuration, the *trans*-configuration for the resulting cyclic compounds **3**–**9**, as well as the *threo*-configuration for the diamino acid **2** can be assigned.

TABLE I

^{1}H NMR coupling constants and IR wavenumbers of imidazolidines entries[a] 1–11



Entry	R	X	R^1	$J_{4,5}$	γ_{OH}[b], 10^{-3} mol l^{-1}	
1	COOMe	CO	H[c]	3.4		
2	COOMe	CO	CH_3	3.8		
3	COOMe	CO	$PhCH_2$[c]	3.7		
4	COOMe	CO	Boc	2.9		
5	CH_2OH	CO	H	3.9	3 620[d]	3 203[e]
6	CH_2OH	CO	CH_3	6.3	3 637[d]	3 337[e]
7	CH_2OH	CO	$PhCH_2$[c]	6.3	3 636[d]	3 400[e]
8	CH_2OH	CO	Boc	5.2	3 629[d]	3 459, 3 421[e]
9	CH_2OH	CS	Boc	5.2	3 630[d]	3 460, 3 221[e]
10	CH_2OH	CH_2	CH_3	7.4	3 628[e]	3 504, 3 325[d]
11	CH_2OH	CH_2	$PhCH_2$	6.3	3 645[e]	3 362, 3 408[d]

[a] For full IR and ^{1}H NMR spectral data of products, see Experimental; [b] $1 \cdot 10^{-3}$ in CCl_4; [c] ref.[3]; [d] weak; [e] strong.

IR spectra of the C-5 hydroxymethyl compounds indicate strong intramolecular hydrogen bonding in the imidazolidinone series (Table I, entries 5–8), as well in the imidazolidinthione (entry 9) and a weaker one for the imidazolidine compounds (entries 10, 11). As can be seen from the ^{1}H NMR spectra of the hydrogen bonded N^1 unsubstituted compound (entry 5), its *trans* *J*(4,5) coupling constant of 3.9 Hz is somewhat lower than the one reported for 5-(hydroxymethyl)-4-phenylimidazolin-2-one[2d] (J_{trans} = 5.2 Hz). This could be due to ring deformation caused by the interaction of the two phenyl substituents at N-3 and C-4, resulting in a preferred axial position of the 4-phenyl group. The effect is similar to the known allylic strain[6,7]. In the case of N^1 substituted compounds (entries 6–11) the *J*(4,5) coupling constants increase to 5.2–7.4 Hz, changing back to approximately the value for the *N*,*N*-unsubstituted compound[2d], thus suppressing the initial role of the "allylic strain". The *J*(4,5) coupling constants for the 5-methoxycarbonyl compounds (entries 1–4) are lower (2.9–3.4 Hz) and independent on the N^1 substitution, probably due to the absence of the hydrogen bond effect.

In conclusion, a convenient synthesis of 1-alkyl-(5-hydroxymethyl)-3,4-diphenylimidazolidines of *trans*-configuration, followed by one-step oxidation and ring cleavage, offers and efficient approach to the corresponding *threo*-2,3-diamino-3-phenylpropanoic acids in high overall yield. The effect of "allylic strain" on and the balancing role of the N^1 substitution in conformations of such highly substituted imidazolidine derivatives are discussed on the basis of ^{1}H NMR and IR spectral data.

EXPERIMENTAL

Melting points were determined on a Kofler apparatus and are not corrected. IR spectra (wavenumbers in cm^{-1}) were recorded on a Bruker ISF 193V spectrometer. ^{1}H NMR spectra were obtained on a Bruker WM 250 MHz spectrometer using Me_4Si as an internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz.

trans-5-(Hydroxymethyl)-3,4-diphenylimidazolidine-2-one (**3**)

A suspension of methyl 3,4-diphenyl-2-oxoimidazolidine-5-carboxylate[3] (237 mg, 0.8 mmol) and $LiAlH_4$ (152 mg, 4.0 mmol) in a mixture of diethyl ether (16 ml) and benzene (16 ml) was stirred at room temperature for 5 h and then hydrolyzed by adding water. Evaporation of the dried (anhydrous $MgSO_4$) ethereal solution afforded the product in a quantitative yield, m.p. 196–198 °C. An analytically pure sample had m.p. 197–198 °C (aqueous ethanol). IR (KBr): 1 670, 3 205 (br). ^{1}H NMR (DMSO-d_6): 3.17–3.31 m, 1 H (5-H); 3.50 d, 2 H, *J* = 5.4 (CH_2O); 4.99 brs, 1 H, D_2O exchangable (OH); 5.19 d, 1 H, *J* = 3.9 (4-H); 6.86–7.46 m, 10 H (H-arom.). For $C_{16}H_{16}N_2O_2$ (268.3) calculated: 71.61% C, 6.01% H, 10.45% N; found: 71.61% C, 6.21% H, 10.6% N.

tert-Butyl *trans*-5-Methyl-3,4-diphenyl-2-oxoimidazolidine-1,5-dicarboxylate (**4**)

To a solution of methyl 2-oxo-3,4-diphenylimidazolidine-5-carboxylate[3] (280 mg, 0.95 mmol) in methylene chloride (2 ml) triethylamine (132 μl, 0.95 mmol), di-*tert*-butyl dicarbonate (413 mg, 1.9 mmol) and 4-(dimethylamino)pyridine (116 mg, 0.95 mmol) were added. The solution was stirred at room temperature under argon for 6 h. Column chromatography on silica gel (hexane–acetone, 95 : 5) afforded the product. Yield 370 mg (99%), m.p. 120–122 °C. An analytically pure sample had m.p. 120–122 °C (ether–hexane). IR ($CHCl_3$): 1 713, 1 744, 1 787. ^{1}H NMR ($CDCl_3$): 1.51 s, 9 H [$C(CH_3)_3$]; 3.87 s, 3 H ($COOCH_3$); 4.48 d, 1 H, *J* = 2.9 (CH); 5.08 d, 1 H, *J* = 2.9 (CH); 7.05–7.45 m, 10 H (H-arom.). For $C_{22}H_{24}N_2O_5$ (396.4) calculated: 66.65% C, 6.10% H, 7.07% N; found: 66.58% C, 6.06% H, 7.08% N.

tert-Butyl *trans*-5-(Hydroxymethyl)-3,4-diphenyl-2-oxoimidazolidine-1-carboxylate (**5**)

A solution of **4** (238 mg, 0.6 mmol) and $NaBH_4$ (228 mg, 6.0 mmol) in methanol (7 ml) was stirred at room temperature for 2 h. Water was added, methanol was evaporated *in vacuo*, the product was filtered off and washed with water. Yield 204 mg (92%), m.p. 159–162 °C. An analytically pure sample had m.p. 160–162 °C (ethanol). IR (KBr): 1 671, 1 719, 1 747. ^{1}H NMR ($CDCl_3$): 1.54 s, 10 H [$C(CH_3)_3$ and OH]; 3.95 d, 2 H, *J* = 3.95 (CH_2O); 4.02–4.07 m, 1 H (5-H); 5.06 d, 1 H, *J* = 5.06 (4-H); 7.02–7.47 m 10 H (H-arom.). For $C_{21}H_{24}N_2O_4$ (368.4) calculated: 68.46% C, 6.57% H, 7.60% N; found: 68.58% C, 6.39% H, 7.82% N.

tert-Butyl *trans*-5-(Hydroxymethyl)-3,4-diphenyl-2-thioxoimidazolidine-1-carboxylate (**6**)

A solution of **5** (221 mg, 0.6 mmol) and Lawesson reagent (122 mg, 0.3 mmol) in toluene (3 ml) was heated at 85 °C under argon for 4 h. Toluene was evaporated *in vacuo* and the product was isolated by column chromatography on silica gel (hexane–acetone, 9 : 1). Yield 138 mg (60%), m.p. 144–146 °C. An analytically pure sample had m.p. 153–155 °C (ether–hexane). IR (KBr): 1 719, 1 746, 3 202. ^{1}H NMR ($CDCl_3$): 1.48 s, 9 H [$C(CH_3)_3$)]; 3.77 m, 1 H (5-H); 4.15 dd, 1 H, *J* = 6.5, 11.1 (CH_2O); 4.30 dd, 1 H, *J* = 4.8, 11.1 (CH_2O); 5.16 d, 2 H, *J* = 5.2 (4-H and OH); 6.96–7.40 m, 10 H (H-arom.). For $C_{21}H_{24}N_2O_3S$ (384.5) calculated: 65.60% C, 6.29% H, 7.29% N; found: 65.78% C, 6.42% H, 7.51% N.

Methyl *trans*-3,4-Diphenyl-1-methyl-2-oxo-3,4-diphenylimidazolidine-5-carboxylate (**7a**)

To a stirred solution of **1** (493 mg, 1.75 mmol) in DMF (10 ml) Ag_2O (103 mg, 4.4 mmol) and methyl iodide (630 μl, 10.0 mmol) were added. The mixture was stirred at room temperature for 6 h, then filtered and evaporated *in vacuo*. The filtered solid was added to the residue, the mixture was extracted with boiling chloroform, filtered and the filtrate was washed with water and dried (anhydrous $MgSO_4$). Evaporation to dryness under reduced pressure and trituration with pentane afforded **7a**. Yield 456 mg (84%), m.p. 110–113 °C. An analytically pure sample had m.p. 115–117 °C. IR (KBr): 1 705, 1 750. ^{1}H NMR ($CDCl_3$): 2.97 s, 3 H (N-CH_3); 3.85 s, 3 H ($COOCH_3$); 3.93 d, 1 H, *J* = 3.8 (5-H); 5.21 d, 1 H, *J* = 3.8 (4-H); 6.94–7.44 m, 10 H (H-arom.). For $C_{18}H_{18}N_2O_3$ (310.3) calculated: 69.66% C, 5.85% H, 9.03% N; found: 69.54% C, 5.64% H, 9.23% N.

trans-5-(Hydroxymethyl)-1-methyl-3,4-diphenylimidazolidine (**8a**)

The title compound was obtained quantitatively from compound **7a** (250 mg, 8.0 mmol) by $LiAlH_4$ reduction according to the procedure described for **3**, m.p. 128–131 °C. An analytically pure sample had m.p. 131–133 °C (benzene–hexane). IR ($CHCl_3$): 3 340, 3 671. ^{1}H NMR ($CDCl_3$): 1.66 brs, 1 H, D_2O exchangable (OH); 2.46 s, 3 H (N-CH_3); 2.72 dt, 1 H, *J* = 7.4, 3.1 (5-H); 3.62 dd, 1 H, *J* = 11.7, 2.9 (CH_2O); 3.76 dd, 1 H, *J* = 11.7, 3.3 (CH_2OH); 4.32 d, 1 H, *J* = 4.9 (CH_2); 4.65 d, 1 H, *J* = 7.4 (4-H); 4.68 d, 1 H, *J* = 5.0 (CH_2); 6.42–7.72 m, 10 H (H-arom.). For $C_{17}H_{20}N_2O$ (268.4) calculated: 76.09% C, 7.51% H, 10.44% N; found: 75.91% C, 7.45% H, 10.4% N.

trans-1-Benzyl-5-(hydroxymethyl)-3,4-diphenylimidazolidine (**8b**)

The title compound was obtained quantitatively from **7b** (ref.[3]) (286 mg, 0.8 mmol) by $LiAlH_4$ reduction, as described for **3**, as an oil. An analytically pure sample had m.p. 39–41 °C (PTC, hexane–acetone, 3 : 2). IR ($CHCl_3$): 3 489. ^{1}H NMR ($CDCl_3$): 2.40 brs, 1 H, D_2O exchangable (OH); 2.46 s, 3 H (N-CH_3); 3.09 dt, 1 H, *J* = 6.25, 32.4 (5-H); 3.64 d, 1 H, *J* = 13.1 (CH_2); 3.63 dd, 1 H, *J* = 4.2, 11.6 (CH_2O); 3.77 dd, 1 H, *J* = 3.8, 11.6 (CH_2O); 4.01 d, 1 H, *J* = 13.1 (CH_2); 4.39 d, 1 H, *J* = 5.8 (CH_2Ph); 4.49 d, 1 H, *J* = 5.8 (CH_2Ph); 4.61 d, 1 H, *J* = 6.3 (4-H); 6.39–7.40 m, 15 H (H-arom.). For $C_{23}H_{24}N_2O$ (344.5) calculated: 80.20% C, 7.02% H, 8.13% N; found: 80.13% C, 6.75% H, 8.35% N.

threo-3-Anilino-2-methylamino-3-phenylpropanoic Acid (**2a**)

trans-5-(Hydroxymethyl)-1-methyl-3,4-diphenylimidazolidine **8a** (134 mg, 0.5 mmol) was added to a stirred solution of CrO_3 (200 mg, 2.0 mmol) in a mixture of glacial acetic acid (1.8 ml) and water (0.2 ml) and the mixture was stirred at room temperature for 24 h. The solution was transferred onto a strong acid cation exchanger, the column was washed with water (40 ml) and ethanol (25 ml) and the amino acid was eluted with 12.5% aqueous NH_3. Ninhydrin-positive fractions were combined and concentrated to dryness *in vacuo* yielding 100 mg (75%) of a product not melting up to 230 °C, which was contaminated with 4.3% Cr (determined by flame AAS). IR (KBr): 1 555, 1 605, 1 645. ^{1}H NMR (D_2O): 1.42 s, 3 H (N-CH_3); 2.95 d, 1 H, *J* = 6.8 (CH); 4.11 d, 1 H, *J* = 6.8. The aromatic signals were overlapped by the H_2O signal. For $C_{16}H_{18}N_2O_2 \cdot 0.2\ Cr(OH)_3$ (290.9) calculated: 8.08% N; found: 7.8% N.

trans-5-(Hydroxymethyl)-1-methyl-3,4-diphenylimidazolidin-2-one (**9**)

Compound **9** was obtained from **7a** (62 mg, 0.2 mmol) by $NaBH_4$ reduction according to the procedure described for **5**. Yield 37 mg (66%), m.p. 178–180 °C. An analytically pure sample had m.p. 179–181 °C (aqueous ethanol). IR (KBr): 1 674, 3 339. ^{1}H NMR ($CDCl_3$): 2.84 s, 3 H (N-CH_3); 3.30 m, 1 H (5-H); 3.71 dd, 1 H, *J* = 12.3, 2.5 (CH_2O); 3.89 dd, 1 H, *J* = 12.2, 3.4 (CH_2O); 5.18 d, 1 H, *J* = 6.3 (4-H); 6.93–7.43 m, 10 H (H-arom.). For $C_{17}H_{18}N_2O_2$ (282.3) calculated: 72.32% C, 6.43% H, 9.92% N; found: 72.19% C, 6.40% H, 10.01% N.

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