Synthesis of imidazolidin-2-one-4-carboxylate and of (tetrahydro)pyrimidin-2-one-5-carboxylate *via* an efficient modification of the Hofmann rearrangement†

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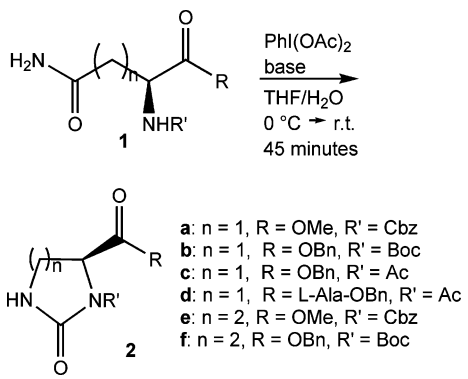
A mild and efficient methodology for the rearrangement of protected asparagine and protected glutamine is reported; good results are obtained with a wide selection of protecting groups.

The Hofmann rearrangement is a well-known reaction that easily allows the transformation of primary amides into amines,[1] utilizing bromine in aqueous basic conditions. Several methods have been described, employing different reagents that are generally able to deliver a positive halogen.[2] However, the classical method for converting a primary carboxamide into an amine using an alkaline solution of bromine can be unsatisfactory and unreliable.[3] Several reagents have also been reported, such as $Pb(OAc)_4$,[4] benzyltrimethylammonium tribromide in aqueous NaOH,[5] and NBS with $Hg(OAc)_2$ or AgOAc in DMF[6] and more recently some solid supported reagents.[7] Analytical and synthetic usefulness have also been demonstrated in peptide sequencing[8] and retro-inverso peptide synthesis.[9]

In the recent years, iodine(III) reagents[10] have been used to perform the same conversions under acidic conditions. The iodine(III) reagents normally employed are $PhI(OCOCF_3)_2$,[11] PhIO–HCO_2H[12] and PhI(OTs)OH,[13] which lead to high yields of the corresponding ammonium salts. Moreover by reacting primary amides with iodine(III) compounds in methanol under basic conditions, the corresponding methyl carbamates are obtained,[14] as methanol behaves both as a solvent and a reagent to trap the intermediate isocyanate.

While our continued interest lies in the synthesis and application of proline analogues,[15] we want to describe herein a method for the rearrangement of protected asparagine and glutamine to imidazolidin-2-one-4-carboxylate and to (tetrahydro)pyrimidin-2-one-5-carboxylate respectively. This reaction has already been reported using NaOCl–NaOH[16] and, more recently, Br_2–NaOH.[17] The reaction times in both cases are quite long and only *N*-carbobenzoxy-L-asparagine can be used as starting material, as *N*-*tert*-butoxy-L-asparagine does not afford the desired product, only by-products. Moreover the authors claim that the reaction is particularly troublesome, as impurities or incomplete conversion make crystallization of the desired product difficult;[17b] of particular importance is the addition of bromine, the amount added proving to be crucial in order to achieve good reaction yields. Furthermore bromine is toxic and its use should be avoided.

In our approach, imidazolidin-2-one-4-carboxylates and (tetrahydro)pyrimidin-2-one-5-carboxylates can be easily obtained in a short time and under very mild conditions starting from protected asparagine or glutamine respectively; this method proved to be quite general because it can be applied to both amino acids in the presence of several protecting groups (Scheme 1). $PhI(OAc)_2$ was the source of iodine(III), as it is cheap and can be easily stored.



Scheme 1 General method for the rearrangement of compounds **1a–f**.

THF is the solvent of choice for this reaction. The reaction was also tested in acetonitrile and dichloromethane, but in these solvents the yield was reduced. The choice of the base was crucial too; the use of DBU was needed for the formation of 5-membered rings **2a–d**, while better results were obtained with diisopropylethylamine for the formation of the 6-membered rings **2e–f**. If DBU is employed for this reaction, the mixture suddenly becomes brownish and a poor yield of the cyclic product is obtained.

In a typical reaction, to a mixture of base (for details see Table 1) and reagent **1a–f** in THF, $PhI(OAc)_2$ was added in one portion. The mixture was stirred for 15 minutes at 0 °C, then a few drops (<0.5 mL) of water were added and the mixture was allowed to stir for an additional 30 minutes. The mixture was concentrated and THF was replaced with ethyl acetate. The product was washed with water and the organic layer was dried and concentrated. Some compounds were obtained pure after crystallization from cyclohexane, while for others, purification by flash chromatography was required.

No by-products are present in the reaction mixture. However if the mixture is allowed to stir for longer reaction times, the yield drops and several by-products are obtained, probably due to

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Table 1 Chemical yields for the rearrangement of compounds **1a–f**

Entry	Product	*n*	Base (equiv.)	Yield (%)
1	**2a**	1	DBU (2)	87
2	**2b**	1	DBU (2)	76
3	**2c**	1	DBU (2)	69
4	**2d**	1	DBU (2)	55
5	**2e**	2	Et(*i*-Pr)$_2$N (3)	79
6	**2f**	2	Et(*i*-Pr)$_2$N (3)	85

partial hydrolysis of the heterocycle. The reaction was successfully made on amounts up to 0.500 g of **1a–f** and can be easily performed on a multigram scale.

The reaction affords the desired compounds in good to high yield, independent of the nature of the protecting group on the amino moiety. Indeed, L-asparagine was protected with carbamates (entries 1 and 2) or with amides (entries 3 and 4) and in each case the desired compound was obtained in a high yield. The reaction was repeated with some samples of protected Cbz-D-Asn-OMe and of Boc-D-Asn-OBn, and the same results were obtained. Remarkably, the dipeptide Ac-L-Ala-L-Asn-OBn was successfully cyclized, thus showing that this method may be employed also for the formation of 2-oxaimidazolidinone-4-carboxylate starting from asparagine moieties belonging to polypeptide chains.

Protected L-glutamine was cyclized under the same reaction conditions: both protecting groups (Cbz, entry 5 and Boc, entry 6) proved to be compatible with this synthetic method, so that (tetrahydro)pyrimidin-2-one-5-carboxylate has been obtained in good yield.

The Boc and Cbz protecting groups can be easily removed following the usual protocol (TFA in dichloromethane and H_2 on Pd/C in methanol respectively).

The most likely reaction mechanism follows a path similar to the classical Hofmann rearrangement.[11c,13a,14a,18] The first step is the formation of the intermediate **3** (Fig. 1), that easily evolves into the corresponding isocyanate **4**. Then **4** is trapped by the nitrogen of the carbamate (or amide) unit, thus forming a thermodynamically driven five or six-membered ring. The introduction of a few drops

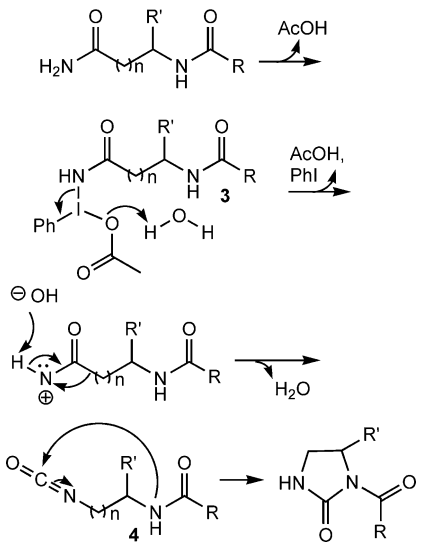

Fig. 1 Reaction pathway for the formation of 2-oxaimidazolidinone ($n = 1$) or of 2-(tetrahydro)pyrimidinone ($n = 2$).

of water after 15 minutes enhances the chemical yield, probably because this favours the formation of isocyanates **4**.

The structure of **2a** was confirmed by an X-ray diffraction study (Fig. 2). As this sample was obtained by cyclization of Cbz-D-Asn-OMe, (***R***)-**2a** was actually analyzed, after crystallization from ethyl acetate.

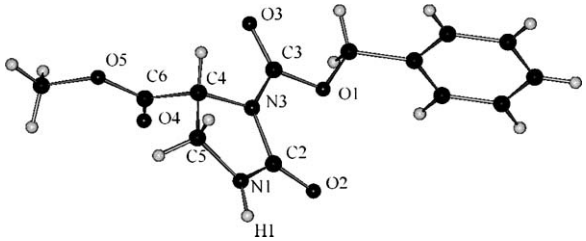

Fig. 2 Molecular structure of (***R***)-**2a**.

The molecular structure of (***R***)-**2a** shows that the imidazolidin-2-one ring is almost planar, as has been found in analogous compounds,[16c] and the sp^3 carbon (C(4)) is 0.09 Å out of the plane defined by the five-membered ring. With respect to this plane, the amido-ester group is slightly twisted [8.1(1)°], while the methyl ester group makes a dihedral angle of 73.1(2)° with the oxoimidazolidine ring (Fig. 3).

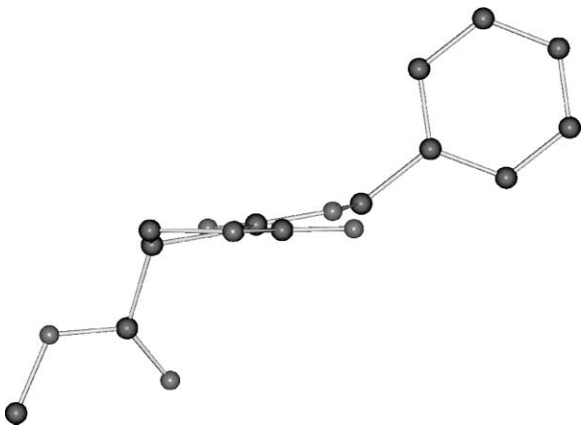

Fig. 3 View of (***R***)-**2a** perpendicular to the oxoimidazolidine ring, showing the almost coplanar endocyclic (C2O2) and exocyclic (C3O3) carbonyls and the orientations of the side-arms.

The methyl ester chain and the benzyl chain lie on opposite sides of the oxoimidazolidine ring; while the two planes defined by the ester group and the phenyl ring are twisted of 12.0°. The absolute configuration of the stereogenic centre at C(4) is *R*.

Conclusions

By means of this modification of the Hofmann rearrangement, protected asparagine and glutamine are easily transformed into imidazolidin-2-one-4-carboxylate and (tetrahydro)-pyrimidin-2-one-5-carboxylate, respectively, in good yield. The reagents are cheap and easily available, the reaction is general, environmentally friendly and the reaction times are very short. The structure of the cyclization product has been confirmed by X-ray diffraction.

Experimental

General notes

Routine NMR spectra were recorded with spectrometers at 300 or 200 MHz (^{1}H NMR) and at 75 or 50 MHz (^{13}C NMR). Chemical shifts are reported in δ values relative to the solvent peak of $CHCl_3$, set at 7.27 ppm. Measurements were carried out in $CDCl_3$ and proton signals were assigned by COSY spectra.

Infrared spectra were recorded with an FT-IR spectrometer. High quality infrared spectra (64 scans) were obtained at 2 cm^{-1} resolution using a 1 mm NaCl solution cell. All spectra were obtained in 3 mM solutions in dry CH_2Cl_2 at 297 K. All compounds were dried *in vacuo* and all the sample preparations were performed in a nitrogen atmosphere.

Melting points were determined in open capillaries and are uncorrected.

Cbz-L-Asn-OH, Boc-L-Asn-OH, Ac-L-Asn-OH, Cbz-L-Gln-OH, Boc-L-Gln-OH were purchased. The benzyl esters were prepared by reaction of the acid with benzyl bromide and TEA in acetone, the methyl esters were prepared by reaction of the acid with $SOCl_2$–MeOH at −15 °C. Ac-L-Asn-L-Ala-OBn was prepared by coupling of Ac-L-Asn-OH and L-Ala-OBn in the presence of HBTU and TEA in acetonitrile.

General method for the synthesis of imidazolidin-2-ones-4-carboxylates 2a–d

To a stirred solution of DBU (2 equiv., 0.9 mmol, 135 μl) in THF (20 mL) was added solid **1a–d** (1 equiv., 0.35 mmol). Upon dissolution, the flask contents were cooled to 0 °C in ice, then $PhI(OAc)_2$ (2 equiv., 0.7 mmol) was added in one portion to the cooled solution and the reaction was left to proceed, stirring at 0 °C for 15 min, after which time a few drops (<1 mL) of H_2O were added and the mixture was stirred for additional 30 min. The reaction mixture was gently concentrated; the resulting yellow oily liquid was dissolved in ethyl acetate and washed with H_2O, dried over Na_2SO_4, filtered, concentrated and dried under vacuum to obtain the crude imidazolidinone. Recrystallization from cyclohexane or silica gel chromatography afforded the pure final product as a solid.

Methyl 3-benzyloxycarbonyl-imidazolidin-2-one-4(*R*)-carboxylate (2a)

Mp = 192 °C; $[\alpha]_D$ +42.0 (*c* 0.1, CH_2Cl_2); IR (CH_2Cl_2, 1 mM): ν = 3450, 1805, 1759, 1698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.45 (dd, 1H, *J* = 3.6, 9.9 Hz, C*H*H-Asn), 3.72 (s, 3H, CH_3), 3.76 (dd, 1H, *J* = 9.9, 10.2 Hz, CH*H*-Asn), 4.82 (dd, 1H, *J* = 3.6, 10.2 Hz, CHα Asn), 5.30 (AB, 2H, *J* = 12.3 Hz OCH_2Ph), 5.96 (bs, 1H, NH), 7.35–7.44 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 40.8, 53.3, 56.1, 68.5, 128.6, 128.7, 128.9, 135.4, 137.7, 151.4, 155.2, 170.5. Anal. Calcd. for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.08; H, 5.04; N, 10.00%.

Benzyl 3-*tert*-butyloxycarbonyl-imidazolidin-2-one-4-(*R*)-carboxylate (2b)

Mp = 181 °C; $[\alpha]_D$ +28.0 (*c* 0.1, CH_2Cl_2); IR (Nujol): ν = 3291, 1801, 1767, 1741 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41 (s, 9H, *t*-Bu), 3.38 (dd, 1H, *J* = 3.6, 9.6 Hz, C*H*H-Asn), 3.73 (dd, 1H, *J* = 9.6, 10.2 Hz, CH*H*-Asn), 4.72 (dd, 1H, *J* = 3.6, 10.2 Hz, CHα-Asn), 5.24 (AB, 2H, *J* = 12.0 Hz OCH_2Ph), 6.91 (bs, 1H, NH), 7.35–7.50 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$,75 MHz): δ 28.1, 40.6, 56.3, 67.8, 83.4, 128.8, 128.9, 135.2, 149.7, 156.5, 170.2. Anal. Calcd. for $C_{16}H_{20}N_2O_5$: C, 59.99; H, 6.29; N, 8.74. Found: C, 60.04; H, 6.31; N, 8.78%.

Benzyl 3-acetyl-imidazolidin-2-one-4(*S*)-carboxylate (2c)

Mp = 187 °C; $[\alpha]_D$ −12.0 (*c* 0.1, CH_2Cl_2); IR (CH_2Cl_2, 1 mM): ν = 3406, 1755, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.56 (s, 3H, CH_3), 3.41 (dd, 1H, *J* = 4.0, 9.6 Hz, C*H*H-Asn), 3.77 (dd, 1H, *J* = 9.6, 10.2 Hz, CH*H*-Asn), 4.91 (dd, 1H, *J* = 4.0, 10.2 Hz, CHα-Asn), 5.15 (bs, 1H, NH), 5.24 (s, 2H, OCH_2Ph), 7.28–7.38 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 27.0, 40.1, 55.0, 67.8, 128.4, 128.7, 128.8, 137.6, 151.1, 169.4. Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.58; H, 5.42; N, 10.69%.

Benzyl 3-L-alanyl-imidazolidin-2-one-4(*S*)-carboxylate (2d)

Mp = 192 °C; $[\alpha]_D$ −31.0 (*c* 0.1, CH_2Cl_2); IR (Nujol): ν = 3423, 1763, 1739, 1700, 1682 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.48 (d, 3H, *J* = 7.2 Hz, CH_3-Ala), 2.58 (s, 3H, CH_3-Ac), 3.61 (dd, 1H, *J* = 9.6, 11.2 Hz, C*H*H-Asn), 3.84 (dd, 1H, *J* = 3.6, 11.2 Hz, CH*H*-Asn), 4.60 (q, 1H, *J* = 7.2 Hz, CHα-Ala), 4.86 (dd, 1H, *J* = 3.6, 9.6 Hz, CHα-Asn), 4.98 (bs, 1H, NH), 5.19 (m, 2H, OCH_2Ph), 6.98 (dq, 1H, *J* = 7.2, 7.2 Hz, NH), 7.37 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$,75 MHz): δ 27.2, 39.4, 48.2, 56.2, 67.6, 128.5, 128.6, 128.9, 135.5, 156.2, 168.4, 172.6, 176.6. Anal. Calcd. for $C_{16}H_{19}N_3O_5$: C, 57.65; H, 5.75; N, 12.61. Found: C, 57.70; H, 5.78; N, 12.68%.

General method for the synthesis of (tetrahydro)pyrimidin-2-one-5-carboxylate 2e–f

To a stirred solution of DIEA (3 equiv., 1.02 mmol, 175 μl) in THF (20 mL) was added solid **1e–f** (1 equiv., 0.35 mmol). Upon dissolution, the flask contents were cooled to 0 °C in ice, then $PhI(OAc)_2$ (2 equiv., 0.68 mmol) was added in one portion to the cooled solution and the reaction was left to proceed, stirring at 0 °C for 15 min, after which time a few drops (<1 mL) of H_2O were added and the mixture was stirred for additional 30 min. The reaction mixture was gently concentrated, the resulting yellow oily liquid was dissolved in ethyl acetate and washed with H_2O, dried over Na_2SO_4, filtered, concentrated and dried under vacuum to obtain the crude pyrimidinone. Purification by flash column chromatography (80 : 20 then 40 : 60 cyclohexane : ethyl acetate as eluent) afforded the pure final product as a solid.

Methyl 3-benzyloxycarbonyl-(tetrahydro)pyrimidin-2-one-5(*S*)-carboxylate (2e)

Mp = 183 °C; $[\alpha]_D$ −18.0 (*c* 0.1, CH_2Cl_2); IR (CH_2Cl_2, 1 mM): ν = 3421, 1745, 1706, 1671 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.62–1.91 (m, 2H, CH_2-Glu), 2.95–3.11 (m, 2H, CH_2-Glu), 3.65 (s, 3H, OCH_3), 4.04–4.13 (m, 1H, CHα-Glu), 5.04 (s, 2H, OCH_2Ph), 5.97 (t, 1H, *J* = 6.0 Hz, NH), 7.30–7.40 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 33.8, 36.6, 51.7, 52.9, 67.5, 128.4, 128.6, 128.9, 136.3, 156.9, 158.2, 173.2. Anal. Calcd. for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.58. Found: C, 57.56; H, 5.55; N, 9.60%.

Benzyl 3-*tert*-butyloxycarbonyl-(tetrahydro)pyrimidin-2-one-5(*S*)-carboxylate (2f)

Mp = 172 °C; $[a]_D$ −26.0 (*c* 0.1, CH_2Cl_2); IR (CH_2Cl_2, 3 mM): ν = 3430, 1745, 1714, 1671 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 1.37 (s, 9H, *t*-Bu), 1.61–1.82 (m, 2H, CH_2-Glu), 2.93–3.08 (m, 2H, CH_2-Glu), 3.96–4.03 (m, 1H, CHα-Glu), 5.11 (AB, 2H, J = 12.6 Hz, OCH_2Ph), 5.92 (t, 1H, J = 5.7 Hz, NH), 7.30–7.38 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.6, 33.7, 36.5, 51.5, 67.4, 80.3, 128.5, 128.7, 128.9, 135.6, 156.2, 158.4, 172.9. Anal. Calcd. for $C_{17}H_2N_2O_5$: C, 61.07; H, 6.63; N, 8.38. Found: C, 61.04; H, 6.60; N, 8.34%.

X-Ray crystallography

Single crystals of methyl 3-benzyloxycarbonyl-2-oxaimidazolidinone-4(*R*)-carboxylate (**2a**) grew as yellow-colourless prisms from ethyl acetate by slow evaporation.

The X-ray intensity data were measured on a Bruker Apex II CCD area detector diffractometer. Cell dimensions and the orientation matrix were initially determined from a least-squares refinement on reflections measured in three sets of 20 exposures, collected in three different ω regions, and eventually refined against all data. For the crystal, a full sphere of reciprocal space was scanned by 0.3 ° ω steps. The software SMART[19] was used for collecting frames of data, indexing reflections and determination of lattice parameters. The collected frames were then processed for integration by the SAINT program,[19] and an empirical absorption correction was applied using SADABS.[20] The structure was solved by direct methods (SIR 97)[21] and subsequent Fourier syntheses and refined by full-matrix least-squares on F2 (SHELXTL),[22] using anisotropic thermal parameters for all non-hydrogen atoms. Two independent molecules were found in the asymmetric unit. All hydrogen atoms were added in calculated positions, included in the final stage of refinement with isotropic thermal parameters, $U(H) = 1.2U\text{eq(C)}$ [$U(H) = 1.5U\text{eq(C-Me)}$], and allowed to ride on their carrier carbons.

Crystal data for 2a. [$C_{13}H_{14}N_2O_5$], M= 278.26, monoclinic, space group P21, a = 9.624(1) Å, b = 7.956(1) Å, c = 9.809(1) Å, β = 118.093(1), U = 662.68 Å^3, Z = 2, μ = 0.08, theta range for data collection 1.29–24.10°, a total of 2950 reflections were measured, and 2499 of them have $I > 2\sigma(I)$.

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