A practical route to $\beta^{2,3}$-amino acids with alkyl side chains

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Abstract

Enantiopure N(Boc)-$\beta^3$-amino nitriles, valuable synthetic intermediates in the multistep homologation of $\alpha$-amino acids, were alkylated using n-BuLi as base. Alkylations afforded easily separable, almost equimolecular mixtures of diastereomeric N(Boc)-protected syn and anti $\beta^{2,3}$-amino nitriles. Suitable manipulations of both cyano and amino groups eventually led to enantiopure N- and/or C-protected $\beta^{2,3}$-amino acids. For example, methanolation using conc. HCl gas in MeOH, provides C-protected $\beta^{2,3}$ amino acids in excellent yields. This methodology is applied to the synthesis of a series N(Boc)-$\beta^{2,3}$-dialkyl amino nitriles derived from L-phenylalanine, D-phenylalanine, L-valine and one C-protected $\beta^{2,3}$ amino acid. We demonstrate an efficient procedure for the preparation of anti and syn $\beta^{2,3}$-amino acids with alkyl side chains, from $\alpha$-amino acids in reasonable yields.

Keywords: Beta-amino acids, Beta-amino nitriles, Alkylation, Homologation, Carbanions

Background

Beta amino acids have shown great potential for a wide range of applications in many fields of organic chemistry in recent years (Juariisti and Soloshonok 2005). The growing interest in this class of compounds, which are widely used in medicinal chemistry forming new secondary structures and as valuable synthetic building blocks, can be better appreciated by database searching (e.g. Sci-Finder). Almost all $\beta^3$-amino acids with proteinogenic side chains are now commercially available, but are quite expensive. Several synthetic procedures have been reported for the preparation of $\beta$-amino acids, and the field has been extensively reviewed (Cole 1994; Liu and Sibi 2002; Weiner et al. 2010).

$\beta^{2,3}$-Amino acids have two substituent at the $\alpha$ (C2) and $\beta$ (C3) positions (Fig. 1). They are relatively rare in nature, although occur as substructures in several bioactive compounds and important metabolites (Juariisti and Soloshonok 2005). These $\beta$-amino acids bearing two side chains are of particular interest for the synthesis of $\beta$-peptides (oligomers of $\beta$-amino acids) in view of their conformation-inducing ability and thereby the ability to afford new foldamers (Seebach et al. 1999; Cheng et al. 2001; Martinek and Fülöp 2012).

$\beta^{2,3}$-Amino acids may be either homochiral (anti- or like-$\beta^{2,3}$-amino acids) or heterochiral (syn- or unlike-$\beta^{2,3}$-amino acids) and it is noteworthy that, when included as building blocks in peptides, the former (1) afford predominantly helical structures, with all substituents in lateral positions, whereas their syn diastereomers (2) adopt an extended conformation, with formation of pleated sheets (Seebach et al. 1999; Balamurugan and Muraleedharan 2015).

A number of synthetic procedure have been proposed for the preparation of $\beta^{2,3}$-amino acids and many of them have been reported recently in an excellent review (Kiss et al. 2015), but very few have been originate from amino acid precursors (Burgess et al. 1993) which have the obvious advantage of transferring pre-existing structural information, such as the nature of side chain and the chirality, into the final products. Among these, the Arndt-Eistert homologation is the most commonly used procedure (Podlech and Seebach 1995). The process involves the conversion of N-protected $\alpha$-amino acid mixed anhydrides into the corresponding $\alpha$-diazoketones using diazomethane, followed by the Wolff rearrangement. It has seen a resurgence in popularity in recent years due to the work carried out at ETH in Zurich,
which has also identified new secondary structures by inserting several ββ residues in homologous peptide sequences (Seebach et al. 2004). However, this procedure is aimed at obtaining ββ-amino acids and only involves intermediate α-diazoketones.

These intermediates have also been used in the preparation of α-methyl ββ-residues via KHMD/HMPA methylation, in modest yields (Yang et al. 2000). Anti ββ-amino acids can be prepared by the alkylation of ββ-amino esters (Estermann and Seebach 1988; Cardillo et al. 1996; Capone et al. 2007). An alternative approach to the asymmetric synthesis of syn and anti ββ-amino acids from non-amino acid precursors, exploits the conjugate addition of a chiral N-protected ββ-amino iodides 4 and ββ-amino nitriles 5 (Scheme 1). This homologation procedure has since been enhanced, and the ββ-amino acids, as well as all homologation intermediates, can be also prepared labeled with isotopic 2H, using NaBD4 in D2O in the reduction step [Caputo and Longobardo 2007].

The homologation intermediate N-protected ββ-amino iodides 4 are extremely useful starting materials for the preparation of new classes of unnatural amino acids (Bolognese et al. 2006; Sureshbabu et al. 2011; Longobardo et al. 2013). Furthermore, N-protected ββ-amino nitriles 5, with different amine Pgs, are substrates in biotransformation reactions to give the corresponding amides and/or amino acids catalyzed by nitrilases and nitrile hydratases (Liljeblad and Kanerva 2006; Veitia et al. 2009).

We therefore considered it timely to report a practical synthetic application of intermediates 5 in a novel approach to the simultaneous synthesis of syn and anti-dialkyl ββ-amino acids (including deuterium labeled compounds) from α-amino acids.

Fig. 1 Anti (1) and syn (2) ββ-amino acids

![Scheme 1 Multistep homologation of α-amino acids to N- and/or C-protected ββ-amino acids](image1.png)

a): NMM/Moc-Cl (0 °C) then NaBH4/H2O;
b): TPP/I2, ImH CH2Cl2, reflux ;
c): KCN, DMSO, 50 °C; d): >12 M HCl in MeOH, 0° C to r.t.
e,f): Boc/Fmoc exchange; f): 8 M HCl aq. in dioxane, reflux
Methods
Solvents, inorganic salts and organic reagents were purchased from commercial resources and used without further purification unless otherwise noted. All of the compounds for which analytical and spectroscopic data are quoted were homogeneous by TLC. TLC analyses were performed using silica gel plates (E. Merck silica gel 60 F-254) and components were visualized by the following methods: ultraviolet light absorbance, iodine adsorbed on silica gel, and ninhydrin spray. Melting points were measured with a Kofler apparatus and are uncorrected. Column chromatography was carried out on silica gel (E. Merck, 70–230 mesh). THF was dried over Na in presence of benzophenone under an Ar atmosphere. All the compounds were characterized by 1H and 13C NMR spectroscopy. NMR spectra were recorded using Varian Inova 500 and Bruker DRX-400 spectrometers: chemical shifts are in ppm and J coupling constants in Hz. High-resolution ES mass spectra were obtained with a Micromass Q-TOF Ultima™ API. Optical rotations were measured with a Jasco 1010 polarimeter (k = 589 nm). One suitable crystal was mounted at room temperature on a Bruker–Nonius Kappa-CCD diffractometer.

General procedure for Alkylation of N(Boc)-β3-amino nitriles
To a magnetically stirred solution of N(Boc)-β3-amino nitrile 5 (R1 = CH2Ph, 1.0 mmol) in anhydrous THF (5 mL), at −78 °C under an argon atmosphere, was added n-BuLi (1.6 M in hexane, 2.2 mmol) dropwise over a few minutes. After 15 min, a solution of benzyl bromide (1.5 mmol) in anhydrous THF (1 mL) was added in one portion, and the mixture was allowed to warm to room temperature over 1 h, before diluting with aq. 0.1 M HCl (10 mL) and extracting with EtOAc (3 × 20 mL). The combined organic layers were washed with water until neutral, and dried (Na2SO4). Evaporation of the solvents under reduced pressure afforded a crude residue consisting of two main products that were readily separated by column chromatography (silica gel, EtOAc-hexane, 1:9). The more mobile product (49 % yield) turned out to be N(Boc)-(2S,3S)-β2,3-dibenzylamino propionitrile (8, Fig. 2). m.p. = 127–128 °C (from Et2O), [α]D25 = −8.1 (c 0.5, CHCl3). 1H NMR (500 MHz, CDCl3) δ: 1.48 (s, 9H, H-Boc), 2.84–3.05 (non resolvable m, 5H, H-2, H-4, H-5), 4.19 (m, 1H, H-3), 4.79 (d, 1H, J = 7.8 Hz, H-NBoc), 7.18–7.34 (m, 10H, H-Ar). 13C NMR (125 MHz, CDCl3) δ: 28.2 (×3), 35.8, 38.8, 40.6, 52.2, 80.2, 119.5, 127.0, 127.2, 128.7 (×4), 128.9 (×4), 136.3, 136.7, 155.3. Anal. Calcd for C22H26N2O2 (350.45): C, 75.40; H, 7.48; N, 7.99. Found: C, 75.37; H, 7.50; N, 8.03. HRMS (ESI), exact mass calcd. for [C22H27N2O2, 351.2067 (M+H)+], found 351.2075.

Fig. 2 N(Boc)-β3-amino nitriles prepared from l-Phe, d-Phe and L-Val
carrier atoms. The final R-factors for 238 refined parameters were R₁ = 0.0717 [on reflections with I > 2σ(I)] and wR₂ = 0.1120 on all the independent reflections. Max and min residual electron densities (eÅ⁻³) = +0.117 and -0.120. The absolute configuration (S) at C2 was assigned by comparison with the chirality at C3, whose absolute configuration (S) is that of the starting L-Phe used for the synthesis of 8. All crystallographic data were deposited with the Cambridge Crystallographic Data Centre, CCDC No. 632994. The second reaction product (45 % yield) was N(Boc)-(2R,3S)-β,ω-dibenzylamino propionitrile (9): m.p. = 132–133 °C (from Et₂O); [α]D²⁵ = -43.2 (c 0.7, CHCl₃); ¹H NMR (500 MHz, CDCl₃): δ = 1.38 (s, 9H, H-Boc), 2.88 (dd, 1H, J = 10.0 and 14.0 Hz, Ha-4), 2.94 (dd, 1H, J = 9.1 and 13.4 Hz, Ha-5), 2.97 (dd, 1H, J = 4.7 and 13.4 Hz, Hb-5), 3.18 (dd, 1H, J = 4.0 and 14.0 Hz, Hb-4), 3.27 (m, 1H, H-2), 4.05 (m, 1H, H-3), 4.60 (d, 1H, J = 7.8 Hz, H-NBoc), 7.21–7.39 (m, 10H, H-Ar). ¹³C NMR (125 MHz, CDCl₃): δ = 28.2 (3x), 35.8, 37.4, 39.6, 51.2, 79.9, 119.9, 127.0, 127.4, 128.9 (x4), 129.2 (x4), 136.3, 136.6, 155.0. The NMR assignments were made using COSY and HSQC experiments. HRMS (ESI), exact mass calcd. for [C₁₈H₂₇N₂O₂, 303.2067 (M⁺ + H)⁺], found 303.2052.

Under the same conditions, the alkylation of N(Boc)-β-amino nitrile ⁵ (R₁ = CH₂Ph) with isopropyl iodide furnished:

14. (25S,3S)-(tert-butoxy carbonylamino)-2-isopropyl-4-phenylbutanenitrile anti 14, 51 %: m.p. = 91–93 °C (Et₂O); [α]D²⁵ = -12.6 ° (c = 0.2, CHCl₃); ¹H-NMR (500 MHz, CDCl₃): δ = 0.97 and 1.09 (d, 6H, J = 6.8 Hz, H-6 and H-7), 1.40 (s, 9H, H-Boc), 1.88–2.00 (m, 1H, H-5), 2.25 (dd, 1H, J = 9.0 and 3.2 Hz, H-2), 2.81 (dd, 1H, J = 13.7 and 8.8 Hz, H₄a), 3.03 (dd, 1H, J = 13.7 and 6.8 Hz, H₄b), 4.18–4.27 (m, 1H, H-3), 4.71 (d, 1H, J = 10.3 Hz, H-NBoc), 7.20–7.35 (m, 5H, H-Phe). ¹³C NMR (125 MHz, CDCl₃): δ = 20.5, 20.9, 28.1 (x3), 29.6, 41.3, 43.8, 50.4, 79.9, 119.3, 126.9, 128.7 (x2), 129.0 (x2), 136.6, 155.1. Anal. Calcld for C₁₉H₂₇N₂O₂ (320.41): C, 71.49; H, 8.67; N, 9.26. Found: C, 71.37; H, 8.50; N, 9.23. HRMS (ESI), exact mass calcd. for [C₁₉H₂₇N₂O₂⁺, 303.2067 (M⁺ + H)⁺], found 303.2049.

15. (2R,3S)-(tert-butoxy carbonylamino)-2-isopropyl-4-phenylbutanenitrile syn 15, 36 %: m.p. = 113–115 °C (Et₂O); [α]D²⁵ = -19.7 ° (c = 0.5, CHCl₃); ¹H-NMR (500 MHz, CDCl₃): δ = 1.10 and 1.16 (d, 6H, J = 6.8 Hz, H-6 and H-7), 1.35 (s, 9H, H-Boc), 1.90–2.04 (m, 1H, H-5), 2.65–2.70 (m, 1H, H-4a), 2.77–2.86 (m, 1H, H-4b), 3.13 (dd, d = 14.2 and 3.4 Hz, 1H, H-2), 4.12 (m, 1H, H-3), 4.46 (d, 1H, J = 8.8 Hz, H-NBoc), 7.20–7.36 (m, 5H, H-Phe). ¹³C NMR (125 MHz, CDCl₃): δ = 19.7, 20.6, 28.1 (x3), 29.6, 37.4, 44.7, 50.3, 79.9, 119.6, 126.8, 128.6 (x2), 129.2 (x2), 136.4, 154.9. HRMS (ESI), exact mass calcd. for [C₁₉H₂₇N₂O₂⁺, 303.2067 (M⁺ + H)⁺], found 303.2083.

Under the same conditions, from the di-deuterated enantiomer of N(Boc)-β-amino nitrile ⁵ (R₁ = CH₂Ph) (Caputo and Longobardo 2007), alkylation with 4-iodochlorobutane provided:

16. (2R,3S)-(tert-butoxy carbonylamino)-2-benzyl-4-methylpentanenitrile syn 13, 30 %: m.p. = 102–103 °C (Et₂O); [α]D²⁵ = -67 ° (c = 0.4, CHCl₃); ¹H-NMR (500 MHz, CDCl₃): δ = 0.95 and 1.00 (d, 6H, J = 6.8 Hz, H-5 and H-6), 1.47 (s, 9H, H-Boc), 2.19–2.20 (m, 1H, H-4), 2.80–2.90 (m, 2H, H-7), 2.88–3.05 (m, 1H, H-3), 3.80–3.90 (m, 1H, H-3), 4.54 (d, J = 10.8, 1H, H-NBoc), 7.26–7.36 (m, 5H, H-Phe). ¹³C NMR (125 MHz, CDCl₃): δ = 15.5, 20.3, 28.3 (x3), 29.6, 35.4, 38.8, 55.6, 80.1, 119.9, 127.2, 128.8 (x2), 128.9 (x2), 136.9, 155.8. HRMS (ESI), exact mass calcd. for C₁₈H₂₇N₂O₂ 303.2067 [(M + H)⁺], found 303.2052.

Under the same conditions, the alkylation of N(Boc)-β-amino nitrile ⁵ (R₁ = CH₂Ph) with isopropyl iodide furnished:
moderate selectivity (from 60:40 to 95:5 anti: syn) observed in the alkylation of β3-amino nitriles has been reported, but the starting nitriles were fully protected with two bulky benzyl groups at the amino nitrogen atom in that case, therefore cannot be directly compared to our work (Reetz et al. 1994).

Various N(Boc)−β2,3-amino nitriles with simple alkyl side chains were prepared under the same conditions. The overall yields of the alkylated products were higher than 80 % in all cases. Details of the synthesis of a series N(Boc)−β2,3-dialkyl amino nitriles derived from L-Phe, d-Phe and l-Val are shown in Fig. 2 and Table 1.

In particular, N(Boc)−β3-amino nitriles 5 (R1 = CH2Ph) was alkylated with benzyl bromide to afford N(Boc)-β2,3-dibenzylamino nitriles anti 8 and syn 9 in 94 % yield. The same alkylation, performed on ent-5, (R1 = CH2Ph from d-Phe) gave 91 % yield of anti 10 (ent-8) and syn 11 (ent-9). Alkylation of 5 with isopropyl iodide (R1 = CH2Ph) gave the corresponding C2-alkylated derivatives 14 and 15 in 87 % yield. Alkylation of 5 [R1 = CH(CH3)2] with benzyl bromide provide the N(Boc)-β2,3-dialkylamino nitriles anti 12 and syn 13 in 90 % yield, that are structural isomers of 14 and 15, which have the same side chains but installed on different C2 and C3 carbons.

Finally, a specially prepared C2-dideuterated N(Boc)-β3-alkyl amino nitrile 5, derived from d-Phe, was alkylated with 4-iodochlorobutane yielding diastereomers 16 and 17 (containing one deuterium atom) in 84 % yield. These derivatives contain a side chain useful for further synthetic elaboration, for example in the preparation of β2,3-amino acids with a lysine side chain (Langenhahn and Gellman 2003).

In all the alkylations studied, single enantiomers were obtained in very good yields after a simple chromatographic separation, as shown in Table 1. The calculation of the dipole moment for compounds 8–17, using the module Chem3D Ultra of ChemDraw software, suggested that for each pair of diastereomers, the anti-stereoisomer was the least polar, and we found that they were eluted first from the silica gel chromatographic columns (EtOAc-Hex 1:9).

Two of the four N(Boc)-β2,3-dibenzylamino nitriles, namely 10 and 11 (prepared from d-Phe) could be readily converted into already known amino acids (Seki et al. 2000), which enabled the assignment of the absolute stereochemistry to the chiral centers of compounds 8–11. Nitrile 10 was converted by methanolysis (14 M HCl in MeOH, 0 °C to room temperature, 12 h) into the corresponding methyl ester hydrochloride 18 in 81 % yield (Scheme 3). The need for a high HCl concentration is necessary for both the transformation of the cyano group and the removal of the amino Pg. The remaining diastereomeric pair, N(Boc)-β2,3-amino nitriles 8 and 9 (prepared

Results and discussion

LDA and metallated-HMDS which are commonly used to produce α-carbanions from N(Boc)-β3-amino esters, turned out to be completely ineffective toward N(Boc)-protected nitriles 5. We found that chiral N(Boc)-β3-amino nitriles are smoothly alkylated at the α-position. The reaction is not at all diastereoselective, hence leads to essentially equimolecular mixtures of syn and anti di-substituted β-amino nitriles. The diastereomers can be easily separated and individually converted into the corresponding N- and/or C-protected β2,3-amino acids. The alkylations were carried out at −78 °C in anhydrous THF, using 2.2 equivalents of n-BuLi per mole of the starting N(Boc)-β3-amino nitrile 5. Under such conditions the resulting lithium diion is rapidly formed and precipitates as a white solid from THF. These diions are quite stable below −65 °C, and rapid quenching with alkyl halides afforded almost equimolecular mixtures of both diastereomeric anti and syn N(Boc)-α,β-dialkyl β-amino nitriles (e.g. 6 and 7 in Scheme 2). One example
from L-Phe) were enantiomers of 10 and 11, respectively, and thus could be assigned the opposite configurations at the chiral center. All the stereochemical assignments were eventually confirmed by X-ray analysis of N(Boc)-β2,3-dibenzylamino nitrile 8 (Fig. 3). The conversions above, along with our existing experience, emphasize the reliability of N(Boc)-β2,3-amino nitriles as intermediates to afford N- and/or C-protected β2,3-amino acids efficiently, preserving the integrity of the chiral centers.

**Conclusions**

The procedure we report here is suitable for the simultaneous preparation of both syn and anti β2,3-amino acids from α-amino acids. The straightforward preparation of the starting chiral N(Boc)-protected β2,3-amino nitriles (including deuterium-labeled derivatives) from commercial N(Boc)-protected proteinogenic α-amino acids is a noteworthy feature of the whole synthetic scheme. The easy preparation of β2,3-amino acids in enantiomeric pure form, with natural or unnatural side chains in position 2 and with the option to introduce other substituents than alkyl groups in this position, starting from low-cost materials, represents a valued synthetic methodology which may find a wide number of applications in the chemistry of amino acids and peptides. In light of the present example, the already mentioned homologation of α-amino acids via β-amino iodides appears to be an effective alternative to the classical Arndt-Eistert homologation procedure, due to the possibility of isolating valuable intermediates, which can be exploited in novel amino acid syntheses.

**Abbreviations**

Boc: tert-butoxycarbonyl; Cbz: benzoyloxy carbonyl; Fmoc: fluorenylmethylxy carbonyl; ImH: imidazole; HMDS: hexamethyldisilazane; HMPA: hexamethyl phosphoramide; LDA: lithium disopropylamide; Moc: methyl carbonyl; NMM: N-methylmorpholine; Pg: protecting group; THF: tetrahydrofuran; TPP: triphenylphosphine.

**Authors’ contributions**

LL design and performed the series of experiments and wrote the manuscript. MDG performed the NMR analysis, including 2D experiments. IdP performed the series of experiments, including purification and characterization of novel molecules. All authors read and approved the final manuscript.

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