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Synthesis of Chiral N-Protected α-Amino Aldehydes by Reduction of N-protected N-Carboxyanhydrides (UNCAs)

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Abstract : A facile one step synthesis of a wide variety of N-protected (Boc, Z, Fmoc) α-amino aldehydes under mild conditions is described. Pure N-protected (Boc, Z, Fmoc) α-amino aldehydes were obtained in high yields by reduction of N-protected (Z, Boc, Fmoc)-N-carboxyanhydrides (UNCAs) with equivalent amounts of lithium tris(tert-butoxy)aluminium hydride [$LiAlH(O\text{-}t\text{-}Bu)_3$] or lithium tris[(3-ethyl-3-pentyl)oxy]aluminium hydride (LTEPA) in THF as solvent. The reaction is simple, rapid and proceeds without detectable racemization.

Optically active N-protected α-amino aldehydes are useful chiral building blocks widely used in the synthesis of pseudopeptides, modified amino acids and natural products[1]. N-protected α-amino aldehydes are mainly obtained by oxidation or reduction of their corresponding N-protected amino acid derivatives[1] (α-amino alcohols, α-amino esters, N'-methyl-N'-methoxy carboxamide). We would like to report on an efficient and simple method for the preparation of chiral N-protected α-amino aldehydes from urethane N-protected carboxyanhydrides (UNCAs). The synthesis of UNCAs has been described by Fuller et al.[2]. UNCAs are crystalline compounds, relatively stable when stored in anhydrous conditions and commercially available. They are extremely reactive compounds which have been used in peptide synthesis in solution[3] and solid phase[4]. They are also precursor material for the synthesis of chiral N-protected β-hydroxy γ-amino acids (e.g. statine derivatives)[5] and N-protected β-amino alcohols[6].

We report in this work on a one step synthesis of N-protected α-amino aldehydes (Boc, Z, FMOC) by reduction of their corresponding UNCAs with lithium tris(terbutyloxy)aluminium hydride [$LiAlH(O\text{-}t\text{-}Bu)_3$] or lithium tris[(3-ethyl-3-pentyl)oxy]aluminium hydride (LTEPA) (Scheme 1). Lithium tris[(3-ethyl-3-pentyl)oxy] aluminium hydride was preferred because it was easier to use (it is available in THF solution) and it yielded a better reproducibility of the experiments in which it was involved. In fact when used in excess, $LiAlH(O\text{-}t\text{-}Bu)_3$

produced some overreduction of the UNCAs leading to a mixture of the expected aldehyde contaminated with a small quantity of the β-amino alcohol. According to the quality of $LiAlH(O\text{-}t\text{-}Bu)_3$, we found difficult to completely control the equivalent amount of $LiAlH(O\text{-}t\text{-}Bu)_3$ which has to be effectively added.

Scheme 1. Synthesis of N-protected α-amino aldehydes from UNCAs

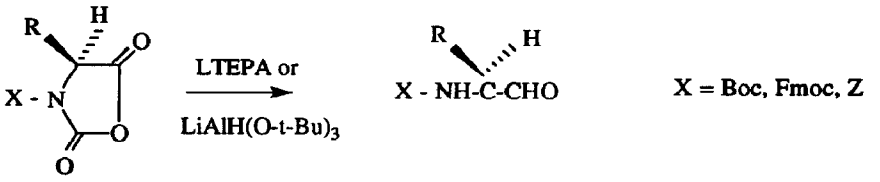


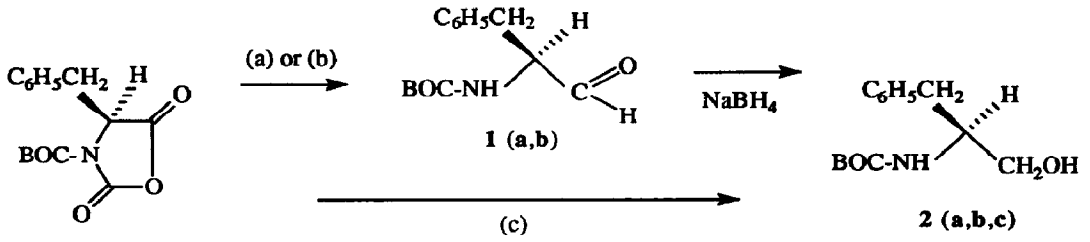
Table 1. Physical characteristics of N-protected α-amino aldehydes prepared from UNCAs by reduction with LTEPA

Aldehydes	Yield %	m.p.°C	$[\alpha]_D$ (c = 1)	Aldehydes	Yield %	m.p.°C	$[\alpha]_D$ (c = 1)
Boc-L-Ala-H	70	84	-19[a]	Boc-L-Val-H	55	oil	-19[a]
Boc-L-Leu-H	81	oil	-35[a]	Boc-D-Val-H	90	oil	+20[a]
Boc-L-Ile-H	56	oil	-20[a]	Boc-L-Phe-H	60	76	-31[a]
Boc-L-Tyr(Bzl)-H	77	84	-5[a]	Boc-L-Met-H	66	oil	-16[a]
Boc-L-Trp-H	78	95-100	-31[a]	Boc-D-Trp-II	80	95-100	+29[a]
Z-L-Val-H	90	oil	-6[a]	Z-L-Phe-H	72	69-71	+21[a]
Fmoc-L-Ala-H	80	145	+10[b]	Fmoc-D-Ala-II	80	145	-11[b]
Fmoc-L-Leu-H	83	65	+10[b]	Fmoc-L-Ile-H	89	85-88	+35[b]
Fmoc-L-Lys(Boc)-H	45	62-65	+2[b]	Fmoc-L-Thr(tBu)-H	84	oil	+36[b]

The purity of the N-protected α-amino aldehydes was checked by HPLC (Merck Hitachi instrument, C_{18} Lichrosorb RP 18, 0.5 μm column, acetonitrile (A) / 0.1% TFA in water (B) as solvent, gradient 10 to 60% (A) in 60 min, flow 1 ml/min, detection 220 nm). Their structure was ascertained by ^1H NMR spectroscopy (100 MHz) and mass spectrometry. [a] Methanol; [b] chloroform.

The usefulness of this method was demonstrated by the synthesis of a series of various N-protected α-amino aldehydes (Boc, Z, Fmoc) from the corresponding UNCAs (Table 1). Reduction of UNCAs with one equivalent of lithium tris[(3-ethyl-3-pentyl)oxy]aluminium hydride (0.5 M THF solution), produced the corresponding configurationally pure aldehydes in reasonable yields. In order to fully characterize these aldehydes, they were purified by flash chromatography on silica gel eluted with organic solvents in the presence of 0.1% pyridine as previously indicated[7].

Scheme 2. Synthesis of N-protected β-aminoalcohols from N-protected α-amino aldehydes

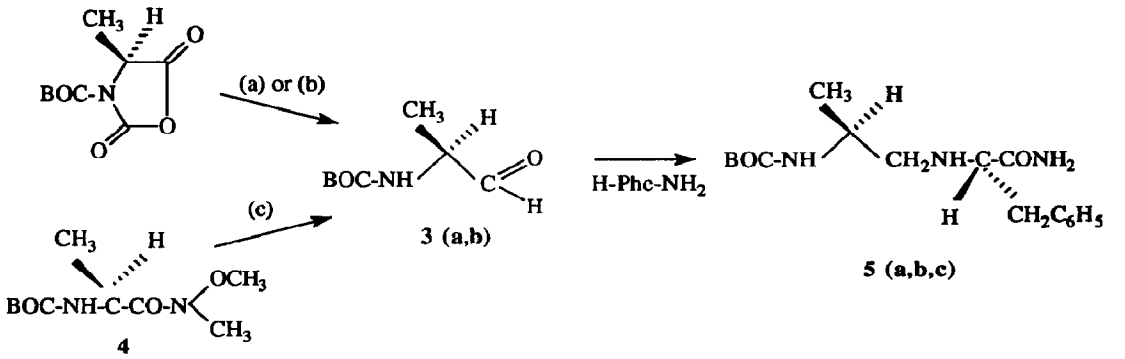


(a) 1 eq LTEPA/THF 0°C; (2a) $[\alpha]_D$ = - 23 (c 1, MeOH); (b) 1.2 eq $LiAlH(O\text{-}t\text{-}Bu)_3$/THF 0°C; (2b) $[\alpha]_D$ = -24 (c 1, MeOH); (c) $NaBH_4$/DME, RT; (2c) $[\alpha]_D$ = - 24 (c 1, MeOH). Compounds 2a, 2b, 2c were identified by ^1H NMR and mass spectrometry.

In order to check that N-protected aldehydes were not racemized when prepared by this method, two control experiments were carried out. In the first experiment, Boc-L-Phe-H **1** was obtained by reduction of the corresponding UNCA (Boc-L-Phe-NCA) : (a) with LTEPA and (b) with $LiAlH(O\text{-}t\text{-}Bu)_3$ (Scheme 2). Isolation, without purification by column chromatography of the aldehyde derivatives (Boc-L-Phe-H **1a, 1b**) resulting from the two reduction experiments, was followed by further reduction into the corresponding alcohols (Boc-Phe-ol **2a, 2b**). The physical characteristics of **2a** and **2b** were compared with those of Boc-Phe-ol **2c** obtained by reduction of the corresponding UNCA with $NaBH_4$ as previously described[6]. All samples were similar (Scheme 2). The same experiments performed from Fmoc-L-Leu-NCA produced Fmoc-L-Leu-ol. In a second set of experiments, the synthesis of a "reduced" dipeptide e.g. Boc-L-Alaψ(CH_2NH)L-Phe-NH_2 (**5**) was carried out by condensation of Boc-L-Ala-H (**3**) used without purification with H-L-Phe-NH_2 (Scheme 3) as previously described[8]. The aldehyde Boc-L-Ala-H (**3**) was prepared by : (a) Reduction of Boc-L-Ala-NCA by LTEPA (**3a**); (b) Reduction of Boc-L-Ala-NCA by $LiAlH(O\text{-}t\text{-}Bu)_3$ (**3b**); (c) Reduction of Boc-L-Ala-N-O-dimethylhydroxamate (**4**) with $AlLiH_4$ (**3c**)[9]. The reduced pseudodipeptides (**5a-c**) obtained by these three different methods showed similar physical characteristics (Scheme 3). On the other hand, ^1H NMR spectra of the authentic (L,L) and (D,L) diastereoisomers of Boc-Alaψ(CH_2NH)Phe-NH_2 prepared via the hydroxamate method[9] were different ($CDCl_3$, Bruker 250 MHz spectrometer). Particularly, the chemical shift of the alanine NH proton (4.17 and 4.28 ppm respectively) and of the doublet of the alanine methyl protons (0.93 and 0.98 ppm respectively) were separated. The ^1H NMR spectra of Boc-L-Alaψ(CH_2NH)L-Phe-NH_2 (**5a, 5b**) prepared from **3a** and **3b** showed a single signal for the Cα and methyl protons of the alanine residue corresponding to the (LL) diastereoisomer, supporting the idea that this method is free of racemization in the limit of the NMR sensitivity.

The same experiments performed by reduction of Fmoc-L-Leu-NCA into the aldehyde Fmoc-L-Leu-H followed by condensation with H-L-Phe-NH_2, yielded Fmoc-L-Leu$\psi(CH_2NH)$L-Phe-NH_2.

Scheme 3. Synthesis of Boc-L-Ala$\psi(CH_2NH)$L-Phe-NH_2 from N-protected α-amino aldehydes



(a) 1 eq LTEPA/THF 0°C; (b) 1.2 eq $LiAlH(O\text{-}t\text{-}Bu)_3$/THF 0°C; (c) $AlLiH_4$/THF 0°C. Compounds **5a, 5b, 5c** were identified by ^1H NMR and mass spectrometry. (**5a**) $[\alpha]_D$ = - 20 (c 1, MeOH); (**5b**) $[\alpha]_D$ = - 20 (c 1, MeOH); (**5c**) $[\alpha]_D$ = - 21 (c 1, MeOH).

This study demonstrated that pure N-protected α-amino aldehydes (Boc, Z or Fmoc) can be easily obtained in one step by reduction of commercially available UNCAs with LTEPA or $LiAlH(O\text{-}t\text{-}Bu)_3$ in mild conditions and in high yields. It showed that N-protected α-amino aldehydes obtained by reduction of UNCAs undergo little or insignificant racemization.

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