Pergamon

Tetrahedron Letters 41 (2000) 37–40

TETRAHEDRON
LETTERS

Synthesis of *N*-protected α-amino aldehydes from their morpholine amide derivatives

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Received 6 August 1999; accepted 21 September 1999

Abstract

A new method for the synthesis of *N*-protected α-amino aldehydes was developed. *N*-Protected α-amino amides of morpholine were easily prepared and then reduced with $LiAlH_4$ to produce clean *N*-protected α-amino aldehydes. This new scheme of synthesis can be used with Boc, Z and Fmoc amino-protecting groups. © 1999 Elsevier Science Ltd. All rights reserved.

Enantiomerically pure α-amino aldehydes are starting materials for asymmetric synthesis of numerous compounds and for pseudopeptide bond formation. They are mainly obtained by oxidation of their corresponding alcohols or by reduction of α-amino acid derivatives with various reducing agents. Reduction of Weinreb amide[1,2] or 3,5-dimethyl pyrazolide[3] of *N*-protected amino acid derivatives is the method of choice compared to the reduction of α-amino esters.[4] The two first derivatives have the major advantage of avoiding alcohol formation during the reduction which proceeds through a stable metal-chelated intermediate. Morpholine amides have already been used with success for nucleophilic acylation reactions from simple carboxylic acids.[5,6] In a recent paper[7] the use of amino acid morpholine amide derivatives for the synthesis of enantiopure α-amino ketones has been described by reaction with organolithium reagents at −78°C. We have investigated the reduction of morpholine amide derivatives of *N*-protected amino acids. In this report we describe the preparation and the use of *N*-protected α-amino morpholine amides to generate the corresponding α-amino aldehydes.

N-Boc and *N*-Z α-amino acids were converted into their morpholine amides by conventional coupling with morpholine and using any method of activation (phosphonium or uronium salts, chloroformiates, DCC/HOBt, etc.) with a preference for phosphonium or uronium salts; when *N*-Fmoc α-amino acids are used, the reaction must go to completion rapidly as morpholine, a secondary amine, is able to cleave the *N*-Fmoc protecting group. In this case we found that the use of isobutylchloroformate (IBCF) as activating agent to preform the mixed anhydride before the addition of morpholine was the best solution.

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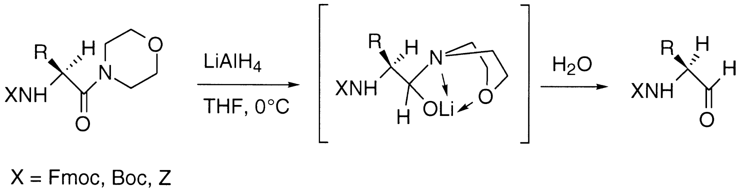
PII: S0040-4039(99)01818-3

Using these conditions, we have prepared *N*-Fmoc α-amino morpholine amides. Reduction of the amides was performed with five equivalents of hydride (that means 1.25 equivalents of $LiAlH_4$) to produce within a short time (10 to 20 min) the corresponding aldehydes in various conditions of temperature (−70°C, −15°C and 0°C). We focused our attention on the eventual formation of the corresponding alcohols and on the optical purity of the aldehydes. At −70°C, the reaction was incomplete even after 90 min while at 0°C it was complete within 20 min. Because traces of alcohol were observed by TLC in all reaction conditions, we preferred to perform the reduction at 0°C. Formation of the corresponding alcohols was very minor, suggesting that a strong stable metal-chelated tetrahedral intermediate was formed (Scheme 1) avoiding the release of the formed aldehydes in the medium and, consequently, an over-reduction of the aldehyde. After hydrolysis, the desired carbonyl components were recovered by a classical work-up. All compounds were characterized by ^1H NMR and mass spectrometry. The enantiomeric purity was checked after purification on silica gel flash chromatography in non-racemizing conditions.[8]



Scheme 1. Reduction of the morpholine amides into aldehydes

This method was tested with some Boc, Z and Fmoc amino acids to check their stability in the reaction conditions. Various *N*-protected α-amino morpholine amides were prepared in good yields using different coupling conditions (Table 1). These amides were then treated at 0°C with $LiAlH_4$ as reducing

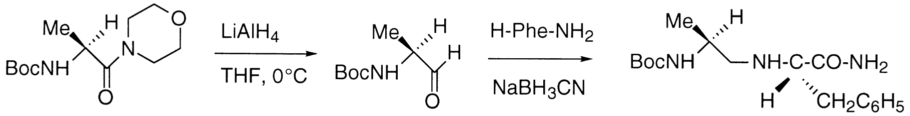
Table 1

Yields and optical purity of morpholine amide derivatives and *N*-protected α-amino aldehydes

Amino-acid derivatives	Morpholine amide derivatives		N-protected α-amino aldehydes[a]	
	Yield (%)	$[\alpha_D]^{20}$	Yield (%)	$[\alpha_D]^{20}$
Boc-Phe	95 [b]	+ 9 [f]	68	- 36 [f]
Boc-Ala	85 [c]	- 27 [f]	75	- 39 [f]
Boc-Leu	91 [b]	- 24 [f]	68	- 41 [f]
Boc-Ser(Bzl)	90 [b]	- 7 [f]	48	+ 2 [f]
Boc-Lys(Z)	82 [b]	- 6 [f]	57	- 2 [f]
Z-Asp(OtBu)	81 [b]	- 45 [f]	73 [e]	N.D.
Z-Phe	88 [b]	+ 11 [f]	53	- 41 [f]
Fmoc-Ala	90 [d]	- 11 [f]	43	+ 13 [g]
Fmoc-Leu	73 [d]	- 19 [f]	43	+ 18 [g]
Fmoc-Phe	90 [d]	+ 4 [f]	50	+ 22 [g]

a: Yields and $[\alpha_D]^{20}$ are given after purification on SiO_2 chromatography as described in the text; b: prepared by coupling with BOP/diisopropylethylamine; c: prepared by coupling with HBTU/ diisopropylethylamine; d: prepared by coupling with IBCF /NMM; e: yield of the crude; f: (c 1, MeOH); g: (c 1, in $CHCl_3$); N.D.: not determinated.

agent to yield after 15–25 min complete reduction of the starting material.[10] After classical work-up, the crudes were examined by TLC and compared in some cases with the crudes resulting from the corresponding Weinreb amide reductions which were synthesized in parallel. These crudes were found as pure as the ones obtained from Weinreb amide reductions and with similar yields. They were purified by silica gel chromatography with eluent systems containing 0.1% pyridine to avoid racemization to measure their optical purity (Table 1). To check that *N*-protected α-amino aldehydes were not racemized when prepared by this method, the synthesis of a reduced dipeptide, e.g. Boc-L-AlaΨ(CH_2NH)L-Phe-NH_2, was carried out by condensation of crude Boc-L-Ala-H with H-L-Phe-NH_2, as previously described[9] (Scheme 2). Examination of the ^1H NMR spectrum showed a single signal for the NH, Cα and methyl protons of the alanine residue corresponding to the (LL) diastereoisomer, supporting the idea that this method was free of racemization during the preparation of the aldehyde. Moreover, the measured $[\alpha]_D$ of the reduced dipeptide was found identical to that of compounds prepared by various methods.[11]



Scheme 2. Synthesis of the reduced dipeptide Boc-L-AlaΨ(CH_2NH)L-Phe-NH_2

In conclusion, this method of preparation of *N*-protected α-amino aldehyde is comparable with the Weinreb amide one and provides an interesting alternative. The high cost of *N*,*O*-dimethylhydroxamate hydrochloride made this new approach attractive since morpholine amides could be easily prepared at low cost. We have also shown the reduction condition compatibility with most of the commonly used *N*-protecting groups.

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10. General method of preparation of the *N*-Boc or *N*-Z morpholine amide derivatives: Boc-Ala-OH (945 mg, 5 mmol) was dissolved in dichloromethane (50 mL), then BOP [(benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate] (2.21 g, 5 mmol) and diisopropylethylamine (DIEA: 1.72 mL, 10 mmol) were added followed by morpholine (0.478 mL, 5.5 mmol). After 90 min stirring, the mixture was concentrated in vacuo and ethyl acetate was added. The organic layer was washed with acidic, then basic and neutral aqueous solutions, dried over sodium sulfate and concentrated in vacuo. The compound obtained as an oil was purified by silica gel flash chromatography. BOP could be replaced by *N*-[(1*H*-benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HBTU) or other phosphonium or uronium salts. Chloroformates were also useful especially in the case of Fmoc-α-amino acids; DCC/HOBt coupling mixture was found less suitable. In the case of coupling with BOP, HBTU, etc. on *N*-Boc or *N*-Z-amino acids, the tertiary amine (DIEA, NEt_3, etc.) could advantageously be replaced by an excess of morpholine (4 equiv.). General method of preparation of the *N*-Fmoc morpholine amide derivatives: Fmoc-Ala-OH (3.11 g, 10 mmol) were dissolved in 25 mL DME and placed at −15°C. IBCF (1.31 mL, 10 mmol) and NMM (1.01 mL, 10 mmol) were then added; the formed precipate was eliminated by filtration and morpholine (0.87 mL, 10 mmol) was added to the solution. After one hour the reaction was complete and treated as previously described. After flash chromatography, 3.4 g of a foam were obtained (yield: 90%). General method of preparation of amino aldehydes: As an example, reduction

of Boc-Phe-morpholine amide is reported. Starting from 3 mmol of amide (1.00 g) dissolved in 30 mL of anhydrous THF and placed under stirring in an ice bath, 47.5 mg (3.75 mmol) of $LiAlH_4$ were added. The reaction was checked by TLC examination (eluent system ethyl acetate/hexane (v/v)) of an aliquot which was separately hydrolyzed. After 15 min, the reaction was hydrolyzed with 5% $KHSO_4$ aqueous solution (5 mL) and extracted with diethyl ether. After classical work-up, 675 mg of a white solid were obtained (yield 91%) which were purified by column chromatography on silica gel with ethyl acetate/hexane (v/v) containing 0.1% pyridine as eluent. Pure material (510 mg) was obtained (68%).

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