A NEW SYNTHETIC APPROACH TO *N*-PROTECTED AMINO ALDEHYDES

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الخلاصة :

تتفاعل الاحماض الأمينية المحمية النيتروجين لمجموعتي (Z, Boc) مع كلٍّ من *N, N*-ثنائي مثيل كلورو إمينيوم كلورايد وثنائي إيثل فوسفور كلوريديت بوجود البيردين لتعطي الانهيدرايد المنشط الذي باختزاله بواسطة كلٍّ من دايبال (DIBAL) أو ثلاثي بيوتوكسي ألمنيوم هيدرايد يؤدى الى الحصول على الالدهيد المقابل .

ABSTRACT

N-Protected (Boc- & Z-) L-α-amino acids have been converted to activated mixed anhydrides by reaction either with *N,N*-dimethylchloroiminium chloride to form (*in situ*) the imidate or with diethyl phosphorochloridate in the presence of pyridine. Subsequent reduction of these anhydrides using either DIBAL or lithium tri-*t*-butoxyaluminum hydride gives the corresponding aldehydes.

Keywords: Organic Chemistry/Amino Acids, Peptides, and Proteins.

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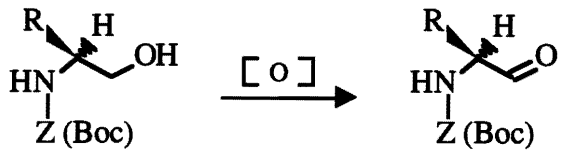
INTRODUCTION

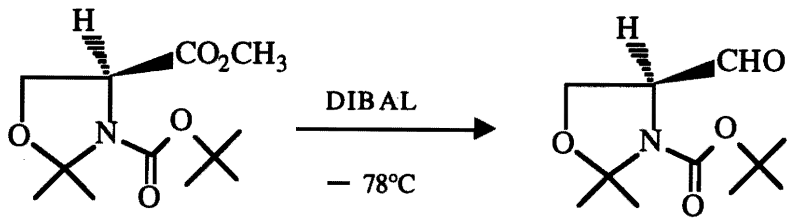
α-Acylamino and α-(alkoxycarbonylamino) aldehydes are of increasing interest due to their inhibitory properties towards some classes of proteolytic enzymes [1] which are able to convert the prochiral aldehydic carbonyl group into a new chiral center. The prochiral aldehydic group provide an interesting access to enantiomerically pure compounds.

α-Amino aldehydes **2** have generally been prepared by oxidation of the corresponding *N*-protected amino alcohols **1**. [2]



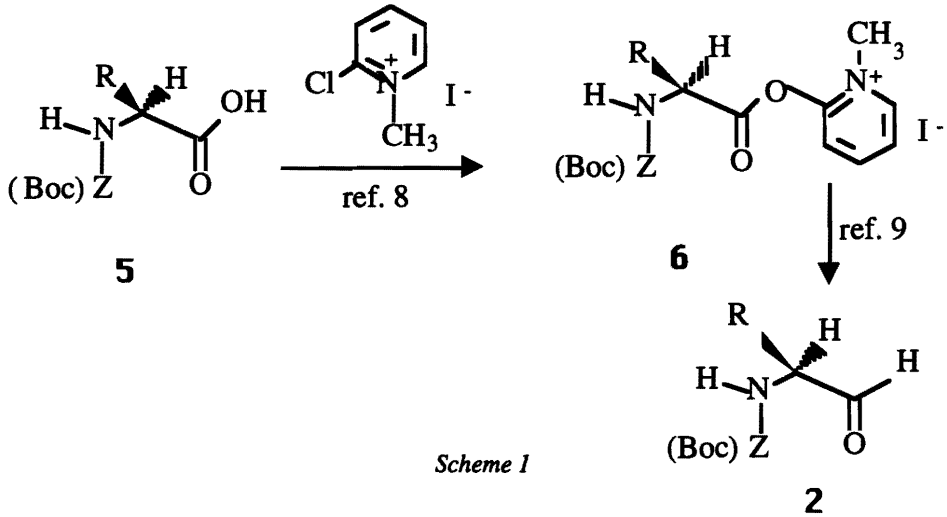
1 **2**

Using diisobutylaluminum hydride as reducing agent for the *N*-protected α-amino ester **3** [3–5] also gives the desired *N*-protected α-amino aldehydes **4** directly.



3 **4**

Recently Fehrentz and Castro [6, 7] developed a new method for the preparation of the α-amino aldehydes *via* the reduction of *N*-methoxy-*N*-methylamides with lithium aluminum hydride. This method has been modified, [8, 9] making use of Mukaiyama reagent (*N*-methyl-2-chloropyridinium iodide) to give **6** as an intermediate [10] instead of (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate (BOP-reagent) for the multistep preparation of the aldehydes (Scheme 1).



5 **6** **2**

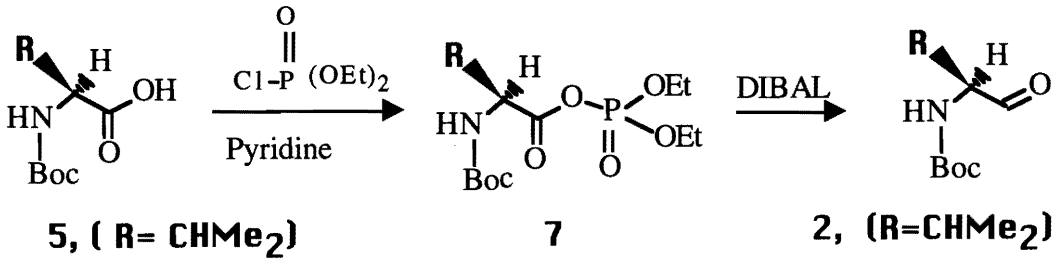
Scheme 1

Very recently, Ohmuri *et al.* [11] prepared α-amino aldehydes by an electrochemical reaction in the presence of triphenylphosphine.

We report herein an alternate synthetic approach to *N*-protected α-amino aldehydes based on the direct conversion of *N*-protected α-amino acids to activated anhydrides.

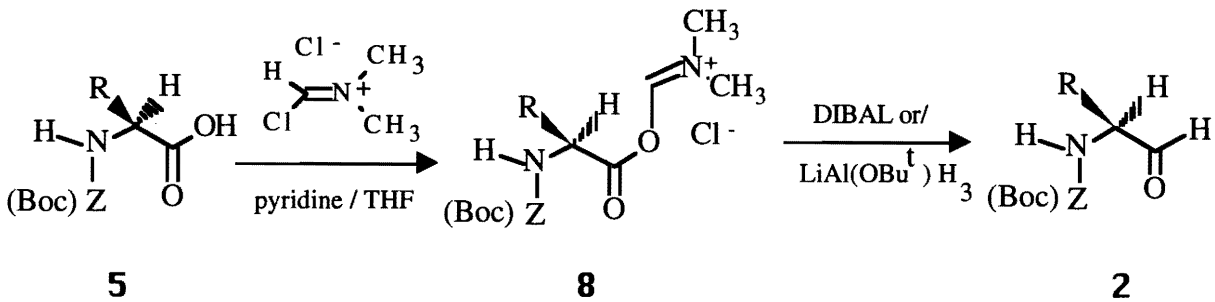
RESULTS AND DISCUSSION

N-Protected valine **5** (R = $CHMe_2$) has been treated with diethylphosphorchloridate in the presence of pyridine. The resulting phosphonate **7** has been reduced (*in situ*) with DIBAL giving the desired aldehyde **2** (R = $CHMe_2$) in 20% yield (Scheme 2).



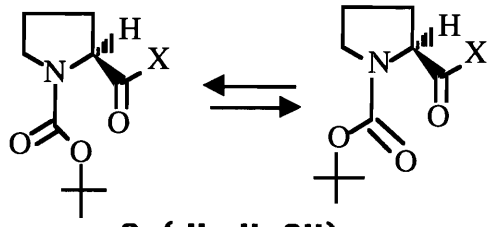
Scheme 2

However, activation with *N,N*-dimethylchloroiminium chloride to form the imidate **8** (*in situ*) [12] and subsequently reduction using either DIBAL or lithium tri-*t*-butoxyaluminum hydride gave the products **2** in fair to good yields (Scheme 3).



Scheme 3

Activation of the carboxylic group of *N*-protected α-amino acids **5** with diethyl chlorophosphate or with *N,N*-dimethylchloroiminium chloride comprises a new method in the synthesis of the corresponding aldehydes and eventually in the peptide synthesis [13]. Reduction of the phosphate mixed anhydride of *N*-Boc.L-valine **5** (R = $CHMe_2$) gave a low, unoptimized yield of **2** (R = $CHMe_2$), probably because of the sensitivity of the (Boc.) protecting group towards hydrochloric acid hydrolysis (see Experimental section), while the imidate mixed anhydride [10] gave the desired aldehydes in acceptable yields. It is interesting to note that the ^1H NMR spectrum of *N*-Boc. L-prolinal **9** (X = H) shows a pair of singlets centered at 1.44 ppm for the $C(CH_3)_3$ group apparently due to restricted rotation of the carbonate moiety. This was also found to be true for the parent *N*-Boc.L-proline **9** (X = OH).



9, (X= H, OH)

EXPERIMENTAL

Infrared spectra were recorded on Perkin–Elmer 457 and 580 infrared spectrometers. NMR spectra ($CDCl_3$) were determined on a Bruker WH 90 spectrometer (Me_4Si internal standard), mass spectra were obtained with a Varian CH 5 (70 eV) mass spectrometer.

General Procedure

Oxalyl chloride (2.5 ml, 10 mmol) was added dropwise to a solution of *N,N*-dimethylformamide (0.08 ml, 10 mmol) in 10 ml of dichloromethane. The mixture was stirred for 1 h and evaporated at reduced pressure at room temperature. The resulting white powder was suspended in 10 ml of tetrahydrofuran (THF) and cooled to –30°C. A solution of the *N*-protected α-amino acid (10 mmol) pretreated with pyridine (10 mmol) in 30 ml of THF was added to the cooled suspension. The reaction mixture was then cooled to –78°C. After one hour stirring, 10 mmol of the reducing agent [DIBAL or $LiAl(OBu^t)_3H$] was added at once. After 20 min stirring, the reaction complex mixture was hydrolyzed by dropwise addition of potassium hydrogen sulfate solution. The organic material was extracted with ether, washed with sodium hydrogen carbonate solution, water, and dried over anhydrous sodium sulfate. Evaporation of the organic solvent gave an oil which was purified by chromatography on silica gel using ethyl acetate/pentane (1:1) as eluent.

Z-L-2-Aminopropanal 2 (R = Me)

Colorless oil (48% yield); ^1H NMR($CDCl_3$): δ ppm 1.35(d, J = 7 Hz, 3H, Me); 4.29(m, J = 7 Hz, 1H, Me CH); 5.11(s, 2H, OCH_2-Ph); 5.22–5.55(br, 1H, NH); 7.34(s, 5H, Ph); 9.43(s, 1H, CHO). ^{13}C NMR($CDCl_3$): δ ppm 199.4(d), 155.9(s), 136.2(s), 128.6(d), 128.2(d), 128.1(d), 67.0(t), 55.9(dd), 14.7(q). MS: 207(M^+, 1%), 178(18%), 134(12%), 91(100%), 84(26%), 75(17%).

N-Z-L-2-Amino-3-phenylpropanal 2 (R = CH_2Ph)

Yield 56%; ^1H NMR($CDCl_3$): δ ppm 3.11(d, J = 7 Hz, 2H); 4.26(m, J = 7 Hz, 1H); 5.08(s, 2H, OCH_2Ph); 5.27(br, 1H, NH); 7.07–7.38(m, 10H, aromatics); 9.6(s, 1H, CHO).

^{13}C NMR($CDCl_3$): δ ppm 198.9(d), 155.9(s), 136.1(s), 135.5(s), [129.6, 129.3, 129.2, 128.7, 128.5, 128.2, 128.1, 127.5, 127.1, 126.8] (aromatic C), 67.1(t), 61.1(dd), 35.3(t).

Boc-L-2-Pyrrolidinecarbaldehyde 9 (X = H)

Yield 40%; ^1H NMR($CDCl_3$): δ ppm 1.44(d, 9H, CMe_3); 1.66–2.22(m, 4H); 3.5(m, J = 6 Hz, 2H); 4.06(m, 1H, NH); 9.33–9.66(m, 1H, CHO). ^{13}C NMR($CDCl_3$): δ ppm 200.1(d), 153.9(s), 80.3(s), 65.0(dd), 46.8(t), 28.3(q), 24.6(t), 23.9(t).

N-Z-L-2-Amino-3-methylbutanal 2 (R = $CHMe_2$)

Yield 70%; ^1H NMR($CDCl_3$): δ ppm 0.93(d, J = 7 Hz, 3H, Me); 0.96(d, J = 7 Hz, 3H, Me); 2.22(m, 1H, CH); 4.55(dd, 1H, CH); 5.10(s, 2H, CH_2); 5.33(d, J = 7 Hz, 1H, NH); 7.31(m, 5H, C_6H_5), 9.61(s, 1H: CHO).

N-Boc-L-2-Amino-3-methylbutanal 2 (R = $CHMe_2$)

A solution of 2.17 g (10 mmol) of *N*-Boc.L-valine and 0.8 ml (10 mmol) of pyridine in 20 ml of THF was added dropwise to a cooled solution of 1.4 ml (10 mmol) of diethyl chlorophosphate in 20 ml of THF under a nitrogen atmosphere in such a way that the temperature does not exceed –40°C. After stirring for 3 hrs at room temperature, the reaction mixture was cooled to –78°C and treated dropwise with 10 ml (1,2 molar solution) of DIBAL in toluene. After one hour at room temperature; the mixture was hydrolyzed using 2N hydrochloric acid solution. The organic phase was extracted with ether, washed with sodium hydrogen carbonate solution, twice with water, and dried over anhydrous sodium sulfate. Evaporation of the organic solvents gave an oily residue which was chromatographed on silica gel (ethyl acetate/pentane 1:1) giving the aldehyde in 20% yield; ^{1}H NMR($CDCl_3$): δ ppm 0.98(t, J = 7 Hz, 6H, 2Me); 1.45(s, 9H, t-Bu); 2.22(m, 1H); 4.22(m, 1H); 5.11(m, 1H); 9.63(s, 1H, CHO). ^{13}C NMR($CDCl_3$): δ ppm 200.4(d); 155.9(s); 80.0(s); 64.7(dd); 29.0(d); 28.3(q); 19.0(q); 17.6(q).

N-Boc-2-Aminoethanal 2 (R = H)

Yield 60%; ^{1}H NMR($CDCl_3$): δ ppm 1.45(s, 9H, 3Me); 4.05(d, J = 5 Hz, 2H, CH_2); 5.04(d, 1H, NH), 9.63(s, 1H, CHO).

N-Z-2-Aminoethanal 2 (R = H)

Yield 50%; ^{1}H NMR($CDCl_3$): δ ppm 4.03(d, J = 7 Hz, 2H, CH_2), 5.10(s, 1H, NH); 5.25(s, 2H, OCH_2); 7.32(s, 5H, C_6H_5); 9.54(s, 1H, CHO).

N-Z-2-Amino-4-methylpentanal 2 (R = $CHMe_2$)

Yield 65%; ^{1}H NMR($CDCl_3$): δ ppm 0.094 (d, 3H, Me); 0.98(d, 3H, Me); 1.30–1.52(m, 2H); 1.65–1.81(m, 1H); 4.77(dt, 1H); 5.10(s, 2d, CH_2); 5.35(d, 1H, NH); 7.11(s, 5H, C_6H_5); 9.61(s, 1H, CHO).

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