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Preparation of N^2-protected amino acid aldehydes via reduction of corresponding acid halides with lithium tris-(tert.butoxy)-aluminium hydride

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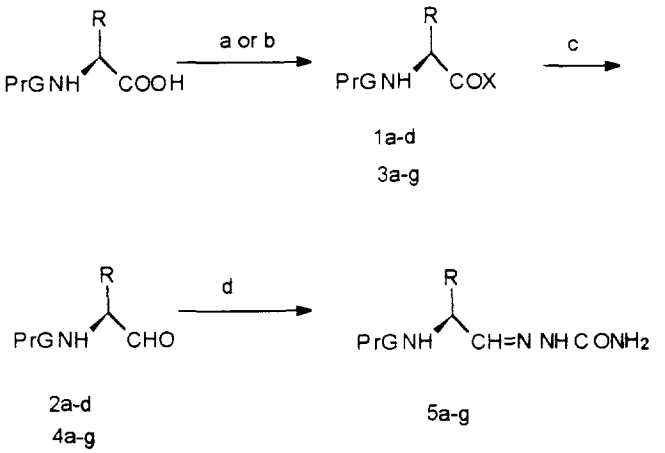
Abstract:*N^2-FMOC amino aldehydes, N^2-BOC amino aldehydes and N^2-Z amino aldehydes are readily preparable from N^2-FMOC amino acid chlorides and N^2-BOC and N^2-Z amino acid fluorides respectively, by reduction with lithium tris-(tert.butoxy)-aluminium hydride.*

N-protected amino aldehydes are important intermediates in the synthesis of many types of proteinase inhibitors containing transition state analogues or peptide bond isosters[1] . Several methods for preparation of these compounds were reported [2-8]

In this contribution , we wish to report the preparation of *N^2-FMOC, N^2-BOC* and *N^2-Z* amino aldehydes via reduction of the corresponding acid halides with lithium tris- (tert.butoxy) -aluminium hydride at low temperature (-70 bis -75°C).

N^2- FMOC amino acid chlorides **1a-d** , generated according to described procedure[9] , gave good yields of corresponding aldehydes **2a-d** with small differences in optical rotation (compared with ref.[8]) . (See scheme 1 , tab.1). *N^2-BOC* and *N^2-Z* amino acid fluorides **3a-g** , described as excellent acylating agents in peptide synthesis were prepared according to Carpino et al. [10]. We have also reduced these compounds under the same conditions as described above, and good yields of aldehydes **4a-g** were obtained Because of considerable differences in the values of optical rotation reported for *N^2 - BOC* amino aldehydes prepared using different methods [11] , all *BOC* and *Z* protected aldehydes were transformed to corresponding semicarbazones **5a-f** which are chromatographically purifiable. Optical rotation of these semicarbazones were compared with literature data.[5,6,12]. (Scheme 1,tab.1)

Scheme 1.



a.$SOCl_2$ / Dichloromethane, (if PrG=FMOC)[8]
b.Cyanuric fluoride Pyridine Dichloromethane (if PrG=BOC,Z)[9]
c.$LiAlH(O\text{-}tBu)_3$ / Tetrahydrofuran / -70°C
d.Semicarbazide hydrochloride AcONa / wt.EtOH[12]

In a typical procedure, the corresponding chloride or fluoride (0.01 mol) was dissolved in dry tetrahydrofuran (20 ml) , and cooled under dry nitrogen and stirring to -75 ° C. A solution of lithium tris- (tert.butoxy)-aluminium hydride (2.51g , 0.01 mol) in dry tetrahydrofuran (25 ml) was slowly added , maintaining the temperature under -70 ° C. After 10 mins stirring , the mixture was poured into 30 ml of 2N HCl (20% citric acid , if BOC protective group was present), extracted three times with ethyl acetate , washed with sat . solution of sodium bicarbonate , brine, dried over sodium sulfate and evaporated in vacuo. Compounds were purified by flash chromatography using 2:1 ethyl acetate-hexane + 0.1 % of pyridine for *FMOC* and *Z*-protected amino aldehydes and 1:1 ethyl acetate hexane + 0.1% of pyridine for *BOC* -protected aminoaldehydes.Then, *BOC* and *Z*-amino aldehydes were transformed to semicarbazones as described [12] and purified by chromatography[5,12].The structure of all compounds were confirmed by ^{1}H and ^{13}C NMR . Yields of aldehydes were ca 60%.

Tab.1. Optical rotations of N^2- protected amino aldehydes **2a-d,4a-g** and semicarbazones **5a-g.**

Cpd.No.	PrG	Amino acid	α_d /(α_d)[ref.a]
2a	FMOC	Ala	-9.4/(-11.6)[7]
2b	FMOC	Val	+16.6/ -
2c	FMOC	Leu	+23.3/(+26.1)[7]
2d	FMOC	Phe	+49.6/(+44.3)[7]
4a	BOC	Ala	-28.7/(-34.1)[8]
4b	BOC	Val	-15.5/(-19.0)[8]
4c	BOC	Leu	-29.3/(-45.7)[8]
4d	BOC	Met	-18.3/(-42.3)[4]
4e	BOC	Phe	-39.3/(-44.4)[8]
4f	BOC	Trp	-6.6/(-8.5)[6]
4g	Z	Phe	-4.5/(-2.7)[12.b]
5a	BOC	Ala	-22.7/(-23.8)[6]
5b	BOC	Val	-14.6/(-14.6)[6]
5c	BOC	Leu	-12.3/(-13.6)[6]
5d	BOC	Met	-13.4/(-12.8)[6]
5e	BOC	Phe	-5.9/(-5.1)[6]
5f	BOC	Trp	-5.1/(-4.7)[6]
5g	Z	Phe	-5.5/(-4.1)[12]

[a] C=1,MeOH

[b] C=2.3

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