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Synthesis of N- and Side chain protected Aspartyl and Glutamyl Aldehyde Derivatives. Reinvestigation of the Reduction of Weinreb Amides.

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Abstract : The reduction of Weinreb amides was reinvestigated in order to find conditions that will allow the synthesis of protected aspartyl and glutamyl aldehydes derivatives useful for peptide and pseudopeptide syntheses. We have demonstrated that lithium tris(tert-butoxy)aluminium hydride [$LiAl(OtBu)_3H$] and lithium tris[(3-ethyl-3-pentyl)oxy]aluminium hydride (LTEPA) can be used to reduce Weinreb amide derivatives into their corresponding aldehydes. In these conditions, it was possible to synthesize N- and side chain protected aspartyl and glutamyl aldehyde derivatives in fairly good conditions.

Pseudopeptides are becoming more and more important as analogs of bioactive peptides or as models for the investigation of structure-function relationships in peptides. The synthesis of peptide bond isosteres mainly relies on the use of amino acid aldehydes as building blocks. Aldehydes are essential in the formation of reduced peptide bonds[1,2], for the synthesis of carba[3] and hydroxyethylene bonds.[4] Several methods for preparation of these compounds were reported including oxidation of the corresponding alcohols[5] or reduction of S-benzyl thioesters[6] but one of the most currently used is the reduction of Weinreb's amide with lithium aluminium hydride.[7,8] This last method is of simple use and can also lead to C-terminal peptide aldehydes[9] which are interesting derivatives as enzyme inhibitors of numerous proteases. The reduction of Weinreb amides with $LiAlH_4$ at 0°C or at lower temperature can generate side products in the presence of sensitive functions, especially when side chain protected aspartyl and glutamyl residues are present. Although the synthesis of N- and side chain protected aspartyl aldehydes from their corresponding N-methoxy-N-methylamide has been described[1,10], these preparations always contained unreacted hydroxamate and some quantities of over reduced derivatives.

In this paper, we describe the synthesis of various N- and side chain protected aspartyl and glutamyl aldehyde derivatives from their corresponding Weinreb amides, by using bulky hydrides. In a first set of experiments, we have checked the stability of *tert*-butyl and cyclohexyl esters, two of the most common side

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chain protecting groups for aspartic and glutamic acids, toward various hydrides. These assays were performed on Boc-Asp(OcHex)-NH_2 and Z-Glu(OtBu)-NH_2 and their stability was checked by reversed phase HPLC after classical work-up. Our observations showed that after 5 h treatment with $LiAlH_4$, the presence of several more polar compounds (including the alcohol function on the side-chain) could be detected. Treatment with bulky hydrides, $LiAl(OtBu)_3H$ or lithium tris[(3-ethyl-3-pentyl)oxy]aluminium hydride (LTEPA) did not affect Boc-Asp(OcHex)-NH_2 or Z-Glu(OtBu)-NH_2. However, the use of DIBAL was not recommended. The results are summarized in Table 1.

Table 1. Study of the stability of Boc-Asp(OcHex)-NH_2 and Z-Glu(OtBu)-NH_2 toward various hydrides.

Compounds	$LiAlH_4$ (1.25 eq) THF/0°C/5h	$LiAl(OtBu)_3H$ (2 eq) THF/O°C or RT/5 h	LTEPA (2 eq) THF/O°C or RT/5 h	DIBAL (1.2 eq) THF/0°C/5 h
Boc-Asp(OcHex)-NH_2	appearance of polar compounds	stable	stable	appearance of polar compounds
Z-Glu(OtBu)-NH_2	appearance of polar compounds	stable	stable	not tested

In a second set of experiments, we have studied the ability of these hydrides to reduce the Weinreb amide derivatives of Boc-Phe, Z-Phe and Boc-Lys(Z). We have demonstrated that $LiAl(OtBu)_3H$ and LTEPA were able to yield the corresponding aldehydes Boc-Phe-H, Z-Phe-H and Boc-Lys(Z)-H in fairly good conditions as compared with $LiAlH_4$. Results are reported in Table 2.

Table 2. Comparison of the Weinreb amide reduction of Boc-Phe, Z-Phe and Boc-Lys(Z) with various hydrides.

Compounds	$LiAlH_4$ (1.25 eq) THF/0°C/30 min	$LiAl(OtBu)_3H$ (2 eq) THF/RT/2 h	LTEPA (2 eq) THF/ RT/4 h
	Yield (%)/$[\alpha]_D$[a]	Yield (%)/$[\alpha]_D$[a]	Yield (%)/$[\alpha]_D$[a]
Boc-Phe-N(Me)OMe	60/-37	62/-34	50/-37
Z-Phe-N(Me)OMe	50/-21	35/-21	30/-21
Boc-Lys(Z)N(Me)OMe	75/-9	77/-12	44/-9

Yields of aldehydes were calculated after a flash chromatography performed as previously described.[6]
[a]*Rotarory power (589 nm) was checked at 22 °C in MeOH.*

In a third set of experiments, we have studied the effects of the reduction of Weinreb amide derivatives of N- and side chain protected aspartyl and glutamyl residues with $LiAlH_4$, $LiAl(OtBu)_3H$ and LTEPA. Treatment of Boc-Asp(OcHex)-N(OMe)Me **1** with $LiAlH_4$ at 0°C yielded a mixture of the expected aldehyde with more polar compounds. When compounds **1** or **2** were treated with $LiAl(OtBu)_3H$ or LTEPA the corresponding aldehydes could be obtained in fairly good conditions. A similar treatment of Z-Asp(OtBu)-N(OMe)Me **3** or Z-Glu(OtBu)-N(OMe)Me **4** produced the corresponding pure aldehydes. However, reduction of Fmoc derivatives of side chain protected aspartic or glutamic acids failed in yielding clean reaction products. The results are summarized in Table 3.

Table 3. Comparison of the Weinreb amide reduction with various hydrides.

Compounds	$LiAlH_4$ (1.25 eq) THF/0°C/0.5 h	$LiAl(OtBu)_3H$ (2 eq) THF/RT/1.5 h	LTEPA (2 eq) THF/ RT/1.5 h
	Yield (%)/$[\alpha]_D$[a]	Yield (%)/$[\alpha]_D$[a]	Yield (%)/$[\alpha]_D$[a]
Boc-Asp(OcHex)-N(Me)OMe **1**	33/-20	50/-20	53/-19
Boc-Glu(OcHex)-N(Me)OMe **2**	40/-30	50/-22	50/-22
Fmoc-Asp(OtBu)-N(Me)OMe	-	32/-3[b]	0[c]
Z-Asp(OtBu)- N(Me)OMe **3**	-	49/-6	54/-6
Z-Glu(OtBu)-N(Me)OMe **4**	-	46/-11	54/-11

Yields of aldehydes were calculated after a flash chromatography performed as previously described.[6]

[a]Rotatory power (589 nm) was checked at 22°C in DMF; [b]aldehyde + starting material; [c]several compounds including fluorene.

All the obtained aldehydes were purified by silica gel chromatography with an eluent system containing 0.1% pyridine[6] and were characterized by mass spectrometry and by ^1H NMR studies.[11] In a typical experiment, Boc-Asp(OCHex)-N(Me)OMe (0.76 g, 2.12 mmol) was dissolved in anhydrous THF at room temperature. $LiAl(OtBu)_3$ 1M in THF (Aldrich) (4.24 ml, 4.24 mmol) was added and the reaction was stirred for 1.5 h. The mixture was then hydrolyzed with a 5% $KHSO_4$ solution and the compound extracted with diethyl ether. The organic layer was washed successively with a saturated solution of $NaHCO_3$, brine, and dried over Na_2SO_4. It was concentrated *in vacuo* to yield an oil (0.46 g, 72%). The amino aldehyde was then

purified by chromatography on silica gel using an AcOEt/hexane solvent system containing 0.1% pyridine[6] to yield 0.30g of pure aldehyde (50%).

In conclusion, we have described in this piece of work the synthesis of N- and side chain protected aspartyl and glutamyl aldehyde derivatives in good conditions with acceptable yields by using bulky hydrides. We have shown that Weinreb amide derivatives of protected amino acids can be converted into their corresponding aldehydes by reduction with $LiAl(OtBu)_3H$ or LTEPA in smooth conditions. Benzyloxycarbonyl and *tert*-butyloxycarbonyl N-protecting groups as well as cyclohexyl and *tert*-butyl esters side chain protecting groups of aspartic and glutamic acids are stable under these reaction conditions, allowing the synthesis of peptide aldehydes having in their sequence such aspartic and glutamic acid derivatives. However, we have recently proposed the synthesis of peptide aldehydes on solid support.[12] In this respect, the use of soluble hydrides could facilitate this chemistry on solid support.

References and notes.

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11. Physical characteristics of the aldehydes: ^1H NMR studies were performed on a 250 MHz Bruker instrument. **Boc-Asp(OcHex)-H**: M+H$^+$: 300; $[\alpha]_D$: -20 (c=1, DMF); ^1H NMR in $CDCl_3$: δ (ppm) 1.43(s, 9H, Boc), 1.3-1.9(3 m, 10H, cyclohexyl ester), 2.77(dd, 1H, Chβ, $J_{C\alpha H\text{-}C\beta H}$=5Hz), 2.97(dd, 1H, Chβ, $J_{C\alpha H\text{-}C\beta H}$=5Hz), 4.32(m, 1H, OCH cyclohexyl ester), 4.72(m, 1H, CHα), 5.56(m, 1H, NH), 9.65(s, 1H, CHO). **Boc-Glu(OcHex)-H**: M+H$^+$: 314; $[\alpha]_D$: -22 (c=1, DMF); ^1H NMR in $CDCl_3$: δ (ppm) 1.40(s, 9H, Boc), 1.3-1.8(3 m, 10H, cyclohexyl ester), 2.1(m, 2H, $CH_2\beta$), 2.40(m, 2H, $CH_2\gamma$), 4.30(m, 1H, OCH cyclohexyl ester), 4.71(m, 1H, CHα), 5.20(m, 1H, NH), 9.60(s, 1H, CHO). **Z-Glu(OtBu)-H**: M+H$^+$: 322; $[\alpha]_D$: -11 (c=1, DMF); ^1H NMR in $CDCl_3$: δ (ppm) 1.38(s, 9H, OtBu), 1.88(m, 2H, $CH_2\beta$), 2.27(m, 2H, $CH_2\gamma$), 4.28(m, 1H, CHα), 5.08(s, 2H, CH_2-Z), 5.50(d, 1H, NH, $J_{NH\text{-}C\alpha H}$ =7Hz), 7.35(s, 5H, ar), 9.55(s, 5H, CHO). **Z-Asp((OtBu)-H**: M+H$^+$: 308; $[\alpha]_D$: -6 (c=1, DMF); ^1H NMR in $CDCl_3$: δ (ppm) 1.46(s, 9H, OtBu), 2.80-3.0(2dd, 2H, $CH_2\beta$, $J_{C\alpha H\text{-}C\beta H}$=4.5Hz), 4.35(m, 1H, CHα), 5.19(s, 2H, CH_2-Z), 5.92(d, 1H, NH), 7.4(s, 5H, ar), 9.70(s,5H, CHO).

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