AN EFFICIENT METHOD FOR PREPARATION OF OPTICALLY ACTIVE *N*-PROTECTED α-AMINO ALDEHYDES FROM *N*-PROTECTED α-AMINO ALCOHOLS

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N-Protected α-amino aldehydes of high optical purity were prepared in excellent yields from corresponding α-amino alcohols by 1,1,1-tris(acetoxy)-1,1-dihydro-1,2-benzoidoxol-3(*H*)-one (periodinane) oxidation.

The preparation of *N*-protected α-amino aldehydes either by reduction of naturally occurring amino acid derivatives or by oxidation of corresponding amino alcohols has been recently reviewed[1]. Retention of optical activity was demonstrated in all cases but optical purity of amino aldehydes was not investigated. Only recently has been reported[2] that the much frequented reduction of *N*-methoxyamides[3] of α-amino acids leads to partial racemization[4] on α-carbon. We have found that neither of published methods[3–7] checked in our laboratory was suitable for fast, by-product free and inexpensive production of optically pure α-amino aldehyde derivatives.

Our preparation of *N*-protected α-amino aldehydes is based on the method of Dess and Martin[8], in which primary or secondary alcohols are oxidized by 1,1,1-tris-(acetoxy)-1,1-dihydro-1,2-benzoiodoxol-3(*H*)-one (periodinane) to aldehydes or ketones. Starting chiral *N*-protected α-amino alcohols* are readily available from corresponding amino acid methyl esters by sodium acetoxyborohydride reduction[10]. The oxidations (Scheme 1) were performed in dichloromethane or chloroform solutions, with 1.2 molar excess of oxidant (for yields and analytical data see Table I). In some experiments the reaction medium was supplemented with *tert*-butyl alcohol which, reportedly[8], aids the oxidation. Nevertheless, even in the absence of *tert*-butyl alcohol the

* Abbreviations used obey the recommendations of IUPAC-IUB Commision on Biochemical Nomenclature[9]. The following additional abbreviations are used: MeOH, methanol; CHF, chloroform; 2,6-DCB, 2,6-dichlorobenzyl; DCM, dichloromethane; Ptg, protecting group.

TABLE I
Yields and analytical data of *N*-protected α-amino aldehydes

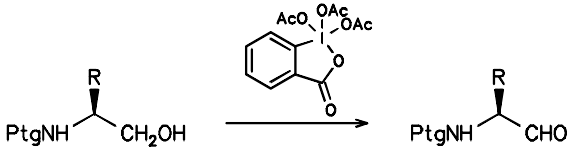
Aldehyde	M.p., °C Yield, %	$[\alpha]_D$, ° *c*, solvent	Formula M.w.	Calculated/Found		
				% C	% H	% N
Boc-L-Ala-al	86 – 88[a]	−36.0[b]	–	–	–	–
	97	0.5, MeOH				
Boc-L-Phe-al	88[c]	−42.2[d]	–	–	–	–
	91	1.0, MeOH				
Boc-L-Pro-al	26 – 32	−70.8	$C_{10}H_{17}NO_3$	60.28	8.60	7.03
	99	1.3, MeOH	199.3	59.83	8.93	7.27
Boc-L-Leu-al	oil	−43.8[e]	–	–	–	–
	98	0.5, MeOH				
Boc-D-Leu-al	oil	+44.4	$C_{11}H_{21}NO_3$	61.37	9.83	6.51
	96	0.5, MeOH	215.3	61.55	9.61	6.77
Boc-L-Nle-al	oil	+39.9	$C_{11}H_{21}NO_3$	61.37	9.83	6.51
	97	0.6, DCM	215.3	61.63	9.56	6.19
Boc-L-Met-al	oil	+12.6[f]	–	–	–	–
	92	0.6, DCM				
Boc-L-Tyr(2,6-DCB)-al	112 – 115	−20.0	$C_{21}H_{23}Cl_2NO_4$	59.44	5.46	3.30
	98	0.6, MeOH	424.3	59.75	5.31	3.52
Z-L-Phe-al	77 – 80[g]	−47.8[h]	–	–	–	–
	90	0.9, MeOH				
Fmoc-L-Leu-al	77 – 79	+22.8	$C_{21}H_{23}NO_3$	74.75	6.87	4.15
	81	0.6, DCM	337.4	74.93	6.76	3.87
Boc-L-Pro-L-Phe-al	amorphous	−47.8	$C_{19}H_{26}N_2O_4$	65.88	7.56	8.09
	92	0.5, CHF	346.4	65.60	7.24	8.00

[a] Ref.[3], m.p. 88 – 89 °C. [b] Ref.[11], $[\alpha]_D$ −40.9°. [c] Ref.[3], m.p. 86 °C. [d] Ref.[3], $[\alpha]_D$ −44.4°. [e] Ref.[11], $[\alpha]_D$ −34.0°. [f] Ref.[11], $[\alpha]_D$ +27.8°. [g] Ref.[11], m.p. 78 – 80 °C. [h] Ref.[12], $[\alpha]_D$ −52.9°.

oxidations were so fast that with most alcohols investigated the reaction course could not be followed even by short-path TLC. Excess of the oxidant was destroyed by aqueous solution of sodium thiosulfate and bicarbonate, which simplified product isolation. The yields of amino aldehydes were almost quantitative except for *S*-benzyl-*N*-(*tert*-butoxycarbonyl)cysteinol which suffered oxidative deprotection with formation of benzaldehyde (88%, as 2,4-dinitrophenylhydrazone).

Optical rotations of several *N*-Boc-amino aldehydes prepared by periodinane method were in good agreement with data published by Fehrenz and Castro[3]. However, we have observed that optical rotations of amino aldehydes in methanol were time-dependent (Table II), e.g. for Boc-Phe-al $[\alpha]_D$ −35.2° at zero time and −42.2° after 48 h. As a plausible mechanism for the optical rotation drift we suggest transformation of α-amino aldehyde carbonyl to a hemiacetal group. Corroboration for this hypothesis we have found in ^{1}H NMR spectra of Boc-L-Phe-al. In $CDCl_3$ solution doublet for CHO appeared at δ 9.62 ppm, but in CD_3OD solution was shifted upfield to δ 3.82 ppm.

Retention of optical activity was observed in all α-amino aldehyde syntheses reported (e.g. refs[3,11]), but its extent has never been investigated. To be assured that there is no racemization in the course of amino alkohol oxidation and/or amino aldehyde



SCHEME 1

TABLE II
Time dependence of optical rotation of *N*-protected α-amino aldehydes in methanol (*c* 0.5) at 23 °C

Aldehyde	$[\alpha]_D$, °	
	t = 0 h	*t* = 48 h
Boc-L-Phe-al	–35.2	–42.2
Boc-L-Leu-al	–46.0	–30.4
Boc-L-Pro-al	–69.8	–74.5
Boc-L-Val-L-Phe-al	–23.8	–34.4

isolation we measured optical rotation of *N*-Boc-phenylalaninol ($[\alpha]_D$ –23.7°, *c* 1.0, methanol) and oxidized it by periodinane. *N*-Boc-phenylalaninal formed ($[\alpha]_D$ –42.4°, *c* 0.5, methanol) afforded by sodium borohydride reduction *N*-Boc-phenylalaninol of the same optical purity ($[\alpha]_D$ –23.3°, *c* 1.0, methanol) as the starting material.

EXPERIMENTAL

Optical rotations were recorded on a Perkin–Elmer 241 automatic polarimeter at 22 °C; the measurements were performed 2 h after dissolution of the amino aldehydes. The melting points were determined on a micro melting point apparatus (Boetius) and are uncorrected. Reagent grade chloroform and dichloromethane (Fluka) were distilled from P_2O_5. Periodinane reagent was prepared as reported in literature[8] and was stored in a dessicator over 3A molecular sieves.

General Procedure for the Oxidation of *N*-Protected α-Amino Alcohols by Periodinane

N-Protected α-amino alcohol (1.0 mmol) in dry dichloromethane (2 ml) was added to a stirred solution of periodinane (530 mg, 1.25 mmol) and *tert*-butyl alcohol (0.10 ml, 1.1 mmol) in dichloromethane (5 ml) at room temperature (cooling with ice-water was necessary if the amount of oxidized alcohol exceeded 5 mmol). When the reaction was finished (usually 10 min) excess of the oxidant was destroyed by addition of a solution of sodium bicarbonate (1 g) and sodium thiosulfate (1 g) in water (15 ml). After 5 min of vigorous stirring the mixture was diluted with dichloromethane (10 ml), organic layer was separated, washed with brine, dried with magnesium sulfate and the solvent was evaporated. Solid residue was triturated with *tert*-butyl methyl ether (5 ml) and filtered through a short pad of silica gel deactivated with water (15%). Pure aldehydes (TLC, HPLC) were obtained by evaporation of the solvent in 81 – 99% yield. Analytical samples were obtained by crystallization from *tert*-butyl methyl ether–hexane.

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