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NEW METHODS AND REAGENTS IN ORGANIC SYNTHESIS. 29.[1)]
A PRACTICAL METHOD FOR THE PREPARATION OF OPTICALLY ACTIVE N-PROTECTED α-AMINO ALDEHYDES AND PEPTIDE ALDEHYDES

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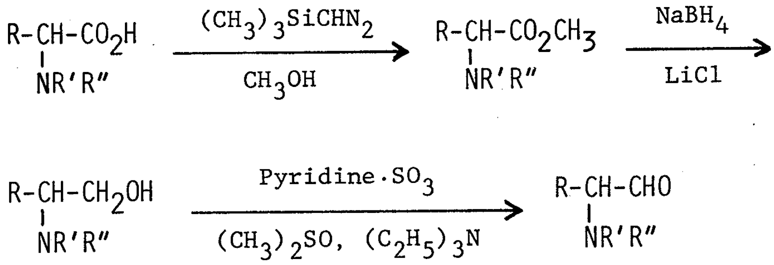
Highly optically active N-protected α-amino aldehydes and peptide aldehydes can be conveniently prepared from the corresponding β-amino alcohols with little or no racemization by the use of a combination of sulfur trioxide-pyridine complex and dimethylsulfoxide in the presence of triethylamine.

KEYWORDS ——— α-amino aldehyde; peptide aldehyde; β-amino alcohol; Parikh-Doering oxidation; sulfur trioxide-pyridine complex; dimethylsulfoxide; enkephalin derivative

Our recent efforts[2)] have achieved a new facile synthesis of prumycin, a 2,4-diaminosugar antibiotic, as an application of the direct C-acylation using diphenyl phosphorazidate(DPPA, $(C_6H_5O)_2P(O)N_3$).[3)] In the synthetic route to prumycin, a conversion of a β-amino alcohol into an α-amino aldehyde without racemization was an indispensable oxidative process. However, reported oxidative procedures[4)] for the preparation of optically active α-amino aldehydes have resulted in low yields and showed great difficulty on purification since α-amino aldehydes are very sensitive to silica gel and racemize very easily during purification. Although reductive procedures for α-amino acid derivatives to α-amino aldehydes have also been reported,[4b,5)] most of them require strict reaction conditions and fail to obtain optically pure α-amino aldehydes directly in good yields. Very recently, Kanellis and co-workers[6)] reported the preparation of optically active N-protected α-amino aldehydes by the reduction of N-protected α-amino acids with borane-tetrahydrofuran, followed by the oxidation of resulting alcohols with pyridinium dichromate. However, it seemed to us that considerable racemization occurred during the oxidation since N-protected α-amino aldehydes were purified on a silica gel column and reported values of optical rotations were too low.

In addition to these investigations, the increasing interest in α-amino aldehydes as useful synthetic intermediates[7)] and peptide aldehydes as inhibitors of proteolytic enzymes[8)] prompted us to seek a practical method for the preparation of optically pure N-protected α-amino aldehydes and peptide aldehydes. We have found that the oxidation of N-protected β-amino alcohols by the use of a combination of sulfur-trioxide-pyridine complex and dimethylsulfoxide in the presence of triethylamine, the Parikh-Doering oxidation,[9)] efficiently affords highly optically active α-amino aldehydes as single products. Starting β-amino alcohols have been very easily prepared from the N-protected α-amino acids by their conversion to the corresponding methyl esters with trimethylsilyldiazomethane in 20 % methanol-benzene,[10)] followed



by the reduction of the esters with sodium borohydride-lithium chloride(1:1, 2 mol. eq.) in ethanol-tetrahydrofuran(3:2) under argon.2)

A typical experimental procedure for the oxidation of β-amino alcohols is as follows(run 6 in Table I): To a stirred solution of Z-L-Phe-ol(N-benzyloxycarbonyl-L-phenylalaninol)11)(570 mg, 2 mmol) and triethylamine(607 mg, 6 mmol) in anhydrous dimethylsulfoxide(6 ml) was added a solution of sulfur trioxide-pyridine complex(955 mg, 6 mmol) in anhydrous dimethylsulfoxide(6 ml) at room temperature. The reaction mixture was stirred for 10 min and poured into ice-water(60 ml). The mixture was extracted with diethyl ether(40 ml x 3) and the organic layer was successively washed with 10 % aqueous citric acid(twice), water(twice), and saturated aqueous sodium bicarbonate, and dried. The solvent was concentrated in vacuo to give Z-L-Phe-al(N-benzyloxycarbonyl-L-phenylalaninal)(567 mg) as a colorless solid. Recrystallization from diethyl ether-hexane afforded colorless needles(480 mg, 85 %).

The results are summarized in Table I. An excess(2.5-4 eq.) of an equal amount of sulfur trioxide-pyridine complex and triethylamine is required to accomplish the reaction quickly and avoid contamination of the starting β-amino alcohols. Little or no racemization was detected in the above procedure, since the N-protected α-amino aldehydes obtained were reconverted to the starting β-amino alcohols with sodium borohydride in ethanol without any loss of their optical purities. The method is quite general since it can be applied to the preparation of N-protected α-amino aldehydes containing various functional groups in the side chains. Methionine and tryptophan derivatives which are susceptible to oxidation12) cause no trouble in the above oxidation process. Furthermore, the method has been revealed to be applied successfully to the preparation of the peptide aldehydes. Enkephalin derivatives having the aldehyde function at their C-terminals(runs 12 and 13) were easily obtained by the oxidation of the corresponding peptide alcohols, which were prepared by the reduction of peptide methyl esters13) with sodium borohydride-lithium chloride(1:1, 4 mol. eq.) in ethanol-tetrahydrofuran(2:1).

The method is very simple and easy to conduct, appears to be quite general, and has advantages over many existing methods. Hence, it will offer a useful and convenient tool for the preparation of synthetically useful α-amino aldehydes and medicinally interesting peptide aldehydes with a high degree of steric homogeneity.

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Table I. Preparation of N-Protected α-Amino Aldehydes and Peptide Aldehydesa)

Run	α-Amino Aldehydeb)	Yield(%)c)	mp(°C)d)	$[\alpha]^{20}_D$	
			(Rec. Solv.)	(C=1, CH_2Cl_2)	(C=1, MeOH)
1	Boc-L-Ala-al	66 (65)	90-92e) (Et_2O-hexane)	+33.9f)	-40.9
2	Boc-L-Val-al	86	oil (154-156)	+19.3g)	-
3	Boc-L-Leu-al	86 (82)	oil (161-163)	+18.4	-34
4	Z-L-Pro-al	96 (87)	oil (133-135)	-78.1	-62.6h)
5	Boc-L-Met-al	90 (74)	oil (140-142)	+27.8	-42.3
6	Z-L-Phe-al	85 (77)	77-79 (Et_2O-hexane)	+44.5	-65.4i)
7	Boc-L-Trp-al	85 (77)	84-87 (Et_2O-hexane)	+42.3	-
8	Boc-L-Tyr(Bzl)-al	81 (72)	98-100 (Et_2O-hexane)	+46.2	-
9	Boc-L-Lys(Z)-al	77 (72)	78-80 (Et_2O-hexane)	+24.9	-13.8
10	Boc-L-Glu(OBzl)-al	88	111-113j) (Et_2O-hexane)	+24.9k)	-
11	Boc-L-Arg(NO_2)-al	92	138-141l) (EtOAc-hexane)	+27.9m)	-n)
12	Boc-L-Tyr-Gly-Gly- L-Phe-L-Leu-al	61o)	160-165 (EtOAc-Et_2O)	-32.9m)	-
13	Boc-L-Tyr-Gly-Gly- L-Phe-L-Met-al	72o)	115-120 (EtOAc-Et_2O)	-32m)	-

a) Unless otherwise stated, reactions were carried out as described in the text. b) Fully characterized by IR(ν^{KBr}_{max} cm^{-1}: 1725-1730(CHO)) and NMR(δ ppm in $CDCl_3$: 9.51-9.67 (1H, s, CHO)) spectral means and elemental analysis. c) Yields of the Parikh-Doering oxidation. Numbers in parentheses are overall yields from N-protected α-amino acids. d) Numbers in parentheses are mps of the corresponding 2,4-dinitrophenylhydrazones. e) Sublimed at 50°C(0.4 mmHg). f) Lit.6a) $[\alpha]^{23}_D$ +1.0°(C=1, CH_2Cl_2); For D-isomer,7e) lit. mp 88°C, lit. $[\alpha]^{20}_D$ -43.2°(C=1.05, $CHCl_3$). g) Lit.6a) $[\alpha]^{23}_D$ +1.2°(C=1, CH_2Cl_2). h) Lit.5d) $[\alpha]^{25}_D$ -45.1°(C=1.5, MeOH). i) Lit.4c) $[\alpha]_D$ -52.88° (C=3.8, MeOH). j) Mp of the hydrate. k) Lit.6a) $[\alpha]^{23}_D$ +6.2°(C=1, CH_2Cl_2). l) Mp of the cyclic hemiacetal. m) Measured in DMF(C=1). n) Lit.5d) $[\alpha]^{25}_D$ -5.3°(C=1.7, MeOH). o) Sulfur trioxide-pyridine complex(4 eq.) and triethylamine(4 eq.) were used.

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