Convenient Synthesis of α-Acylamino Aldehydes

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Summary The reduction by di-isobutylaluminium hydride of *N*-blocked amino acid imidazolides gives good yields of α-acylamino aldehydes, the optical purity of which is higher than those previously reported, but a check of one aldehyde prepared showed only 60% optical purity; the chemical shifts at the aldehydo ^{13}C and ^{1}H resonances are reported.

SEVERAL methods for the conversion of *N*-acyl amino acid derivatives into the corresponding aldehydes have been reported recently. Yamada[1] showed that amino acid mixed anhydrides could be hydrogenated to give aldehydes, while Umezawa[2] *et al.* used $LiAlH_4$ to convert arginine lactam derivatives into the aldehyde protease inhibitor leupeptin. Later, Ito[3] found that *N*-benzyloxycarbonyl amino acid esters could be converted into aldehydes by reduction with Bu^i_2AlH and Rich[4] used this same method in a recent synthesis of statine. In Ito's work,[3] the aldehyde function was protected by conversion into the semicarbazone while the amino group was deblocked and coupled to form the desired peptide. Deprotection of the aldehyde function then required difficult treatment with a formaldehyde–HCl reagent.

Since the reduction of aminoacylimidazolides with $LiAlH_4$ has also been used[5] to make amino aldehydes, we examined the use of the milder and more convenient agent Bu^i_2AlH in this reaction. An acid, α-acylamino acid, or *N*-blocked peptide acid, was converted into the acylimidazolide intermediate with carbonyl di-imidazole and the reduction with Bu^i_2AlH was carried out *in situ* rapidly and conveniently. Typically, to a stirred solution of an *N*-blocked amino acid (5 mmol) in 25 ml of dry toluene (or tetrahydrofuran) under nitrogen was added di-imidazolyl ketone (5·5 mmol) at 0 °C. The mixture was stirred for 10 min, cooled to −40 °C, and Bu^i_2AlH in hexane (10—15 mmol) was added dropwise. The mixture was stirred for 30 min and excess of Bu^i_2AlH was decomposed by addition of 30 ml of 1N HCl [5% citric acid for the Boc amino acid (**4**)]. The resulting mixture was allowed to warm to room temperature and the organic layer was separated. The aqueous layer was extracted twice with ethyl acetate (25 ml) and the combined organic extracts were washed with water, saturated $NaHCO_3$ solution, and saturated NaCl solution, and dried over anhydrous $MgSO_4$. Removal of solvent gave the crude *N*-blocked amino aldehyde which was chromatographed on a silica gel column (20 g) using chloroform.

TABLE 1

Acid RCO_2H	% Yield of aldehyde RCHO	$[\alpha]_D^{25}$ (*C*, MeOH)
$PhCH_2CO_2H$ (**1**)	83	—
$PhCH{=}CHCO_2H$ (**2**)	80[a]	—
$HN{=}C(NHNO_2)NH[CH_2]_3CH(NHZ)CO_2H$ (**3**)[b]	63	−1·46° (1·7)[c]
$HN{=}C(NHNO_2)NH[CH_2]_3CH(NHBoc)CO_2H$ (**4**)[d]	57[h]	−5·3° (1·7)
$PhCH_2CH(NHZ)CO_2H$ (**5**)	70	−23·3° (0·84)[e]
Z–N⌜$[CH_2]_3$⌝$CHCO_2H$ (**6**)	52	−45·1° (1·5)[f]
$Z{-}NHCH(Bu^i)CO_2H$ (**7**)	63[i]	−22·8° (0·74)[g]
$PhCH_2CH(NHZ)CONHCH(CO_2H)[CH_2]_3NHC(NHNO_2){=}NH$ (**8**)	42	−10° (0·51)

[a] Contained 20% cinnamyl alcohol by n.m.r. spectroscopy. [b] Z = benzyloxycarbonyl. [c] Lit.[5] $[\alpha]_D$ − 1·4° (*C* 2·1, MeOH). [d] Boc = t-butyloxycarbonyl. [e] Lit.[5] $[\alpha]_D$ − 2·7° (*C* 2·3, MeOH). [f] Lit.[5] $[\alpha]_D$ − 40·8° (*C* 1·9, MeOH). [g] Lit.[5] $[\alpha]_D$ − 3·1° (*C* 1·4, MeOH). [h] Elemental analysis of 2,4-dinitrophenylhydrazone was correct. [i] Correct elemental analysis as monohydrate.

Table 1 lists the aldehydes so far prepared by this method. Compounds (**1**) and (**2**) were used as saturated and unsaturated examples and (**3**), (**5**), (**6**), and (**7**) as amino acid derivatives which have been previously reduced.[3a] The Boc amino acid (**4**) was prepared in order to show the stability of the Boc protecting group to the reduction conditions and to allow for the preparation of the deblocked amino aldehyde if so desired.† These compounds were all purified by silica gel chromatography (2—4 h required) and, in spite of this, have higher rotations than those previously reported. Shimizu *et al.* reported[5] that silica gel caused observable racemization of α-acylamino aldehydes. In order to check the optical purity of one of our products, ZNHCH(Bu^t)CHO was both reduced with $NaBH_4$ to *N*-benzyloxycarbonyl leucinol and oxidized to ZNHCH(Bu^t)CO_2H with $KMnO_4$. Both the alcohol and the acid were found to be 60% optically pure, indicating that the maximum optical pnrity of *our* ZNHCH(Bu^t)CHO was only 60% and that the previously reported product had a very low optical purity (*ca.* 8%). These results throw doubt on the optical purity of all the amino aldehydes so far reported (including ours) and indicate that optically pure amino aldehydes may prove to be very difficult to prepare.

TABLE 2

	^{13}CHO	CHO
$HN{=}C(NHNO_2)NH[CH_2]_3CH(NHZ)CHO$	75·00	5·73 (q)
$PhCH_2CH(NHZ)CHO$	198·60	9·53 (s)
Z–N$[CH_2]_3$CHCHO	199·53	9·46 (d)
Z–NHCH(Bu^t)CHO	200·13	9·50 (s)

Table 2 reports the ^{13}C chemical shift, of some of the aldehyde carbon atoms and protons observed in this series. The low field position of the aldehyde carbon resonances is very useful for diagnostic purposes. It is striking that no coupling of the aldehyde proton is observed (60 MHz instrument) for phenylalaninal and leucinal, while prolinal shows only a small coupling (J 4 Hz). This may indicate that the angle[6] ψ approximates to +60° (causing the aldehyde and α-protons to subtend a 90° angle) in the preferred conformation of these α-amino aldehydes. The argininal derivative is known[3,5] to exist as a cyclic hemiaminal and, consequently, has no true aldehyde function. This is confirmed also by the high-field position of the ^{13}C and ^{1}H resonances for this group.

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† Since the nitro-argininal derivatives are cyclic carbinolamines (ref. 5), deblocking of the reduction product in HBr–HOAc may lead to replacement of the methanolic hydroxy group by a bromine atom. The milder conditions required for Boc removal may avoid this complication.

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