ISSN: 0974 - 7516 Volume 11 Issue 2

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 11(2), 2015 [041-044]

Reduction of α-Amino acids to chiral amino alcohols with potassium borohydride and aluminum chloride

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ABSTRACT

The formation of chiral amino alcohols by reduction of amino acids has been widely studied due to their important applications. α-Amino acids were reduced through $KBH_4/AlCl_3$ under mild or reflux reactions conditions, providing corresponding aminio alcohols in high yield and purity. It suggested that 1.4 equivalent of $AlCl_3$ was adequate to reduce the amino acids to the corresponding β-amino alcohol. An improved, convenient procedure that reduces amino acids through $KBH_4/AlCl_3$ to the corresponding chiral amino alcohols in excellent yields under mild conditions has been found.

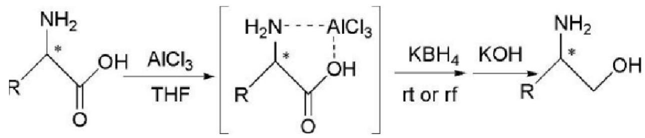
KEYWORDS

Amino acids;
Chiral amino alcohols;
$KBH_4/AlCl_3$;
Reduction.

INTRODUCTION

Chiral amino alcohols, especially â-chiral amino alcohols, are widely used in the syntheses of pharmaceuticals[1,2,3] and insecticidal compounds[4], in various asymmetric syntheses[5-9] and in other applications. In consideration of their extensive applications, some â-chiral amino alcohols are used as chiral auxiliaries by our group. It is a good method that they are acquired directly through the reduction of the corresponding naturally occurring amino acids. Many reduction systems have been reported using expensive complex metal hydrides like $LiAlH_4$[10,11] or $NaBH_4$ in conjunction with strong acids like $BF_3{\cdot}Et_2O$[12], H_2SO_4[13,14,15], I_2[16] or $(CH_3)_3SiCl$[13,17] which may be expensive or unsafe. The $LiAlH_4$ procedure is one of the most commonly used techniques but on large scale still suffers from the disadvantage of cost, inflammability[16]. In the next place, some acids like $BF_3{\cdot}Et_2O$, I_2 or $(CH_3)_3SiCl$ are expensive and unsafe to use. Narasimhan[18] et al reported the reduction of amino acids by zinc borohydride. Though zinc borohydride reduces amino acids with only stoichiometric amounts of hydride, it needs more operations and the stratification of liquid-liquid is hard because of zinc hydroxide emulsion when extracting. Brown[19] et al reported the reduction of aliphatic and aromatic carboxylic acids by $NaBH_4/AlCl_3$ under room temperature or 75!. It is a simple and effective method for tow carboxylic acids. On the other hand, $NaBH_4(KBH_4)$ and $AlCl_3$ is convenient, less expensive, and safer to use. But for all this, there have been no reports describing the reduction of á-amino acids via $NaBH_4$ $(KBH_4)/AlCl_3$ system.

Recently $KBH_4/AlCl_3$ system have been used by us for the reduction of á-amino acids, providing corresponding aminio alcohols in high yield and purity



Scheme 1

under mild or reflux reactions conditions (Scheme 1). The results are listed in TABLE 1. Taking the reduction of L-Phenylalanine, for example, a typical experimental procedure is described below.

EXPERIMENTAL

All the *á*-chiral amino acids were directly purchased from Aldrich. The reaction process was monitored by GF254 TLC using petroleum methanol/acetic acid /2% ninhydrin-ethanol (97:3:0.1 v/v/v) as the eluant[20]. Melting points were recorded by a microscopy apparatus (SGWX-4) and are uncorrected. Polarimetric measurements were taken on an automatic polarimeter. All the solvents were freshly distilled. The products were also characterised by com-parison of their melting points and optical rotation with the literature values.

General procedure for reduction of amino acids

(a) Reaction 1

A stirted suspension of L-Phenyl-alanine (1.65g, 0.010mol) in THF (30ml), $AlCl_3$(fresh, 1.86, 0.014mol) was partially added at such a rate as to maintain the reaction mixture below 20! (addition time 0.5h). The flask was immersed in a water bath, and KBH_4(1.13g, 0.021mol) was added partially. Slowly heat up to 25!. Stirring of the reaction mixture was continued at room temperature until TLC on silica gel shows the absence of starting material, and distilled water (5ml) was added carefully to destroy excess BH_3. The mixture was basified with 20% aqueous KOH to pH 10 and stirred for 1 h. The organic phase were separated and the aqueous layer extracted with 2×12 mL of methylene chloride. The combined organic extracts were dried over sodium sulfate and concentrated in vacuo, affording a white solid by rotary evaporation. The solid was recrystallized from toluene to yield 0.642g (85%) of the pure product as colorless crystals: mp 90-92°C.

(b) Reaction 2

A stirted suspension of L-Phenyl-alanine (1.65g, 0.010mol) in THF (30ml), $AlCl_3$ (fresh, 1.86, 0.014mol) was partially added at such a rate as to maintain the reaction mixture below 20! (addition time 0.5h). The flask was immersed in a water bath, and KBH_4(1.13g, 0.021mol) was added partially. Slowly heat up to reflux. The flask was heated to reflux until TLC on silica gel shows the absence of starting material and then cooled to room temperature, and distilled water (5ml) was added carefully to destroy excess BH_3. The mixture was basified with 20% aqueous KOH to pH 10 and stirred for 1h. The organic phase were separated and the aqueous layer extracted with 2×12 mL of methylene chloride. The combined organic extracts were dried over

TABLE 1 : Reduction of *α*-chiral amino acids to *β*-chiral amino alcohols

Entry	Product	Yield (25℃/65℃) (%)	m.p.(℃) /lit[19]	$[\alpha]_D^{20}$/lit[19]
1	L-Phenylalaninol	85/95	93-95/ 92-95	-22.3 /-22 (c=1.2,1N HCl)
2	D-Phenylalaninol	84/95	94-95/ 93-95[21]	+22.3 /+23[21] (c=1.2,1N HCl)
3	L-Phenylglycinol	85/92	75-76/ 74-76	+31/+31 (c=0.75,1N HCl)
4	D-Phenylglycinol	84/93	74-76/ 75-77[16]	-31 /-32[16] (0.75, l M HC1)
5	L-Prolinol	84/86	73-76/ 73-76 (2mmHg)^a	+31/+31 (c=1, $C_6H_5CH_3$)
6	L-tert-Leucinol	84/87	33-34/ 32-34	+37/+37 (c=1.5, EtOH)
7	L-Isoleucinol	84/87	28-30/ 28-30	+5.0/+4.9 (c=1.6, EtOH)
8	L-Isoleucinol	85/89	198-200/ 197-200^a	+3.9/+3.7 (c=9, EtOH)
9	L-Valinol	86/89	29-30/ 29-30	+17/+17 (c=10, EtOH)
10	D-Alaninol	69/71	173-175/ 171-174^a	-17/-16.5 (neat)
11	L-Methioninol	84/87	33-35/ 34-36	-12/-12 (c=1.4, EtOH)

^{a} **Boiling points were determined**

TABLE 2 : Effect of the different molar ratios (AlCl3:amino acid) to L-Phenylalanine

Entry	Substrate (mmol)	KBH4 (mmol)	AlCl3 (mmol)	AlCl3/ Substrate	Yield (%)
1	10	21	9	0.9/1	76
2	10	21	10	1/1	81
3	10	21	11	1.1/1	86
4	10	21	12	1.2/1	90
5	10	21	13	1.3/1	93
6	10	21	14	1.4/1	95
7	10	21	15	1.5/1	95

sodium sulfate and concentrated in vacuo, affording a white solid by rotary evaporation. The solid was recrystallized from toluene to yield 0.718g (95%) of the pure product as colorless crystals: mp 90-92°C.

RESULTS AND DISCUSSION

The use of Lewis acid is a common and convenient method for increasing the reductive efficiency of KBH_4[20]. With the addition of aluminium trichloride, system was gradually clarified. It was speculated that amino acids and aluminium chloride had formed complex compounds, causing them to dissolve in tetrahydrofuran Scheme 1. It was found that reaction 2 took less time and yielded higher to reduce á-amino acids in comparison with reaction 1. It was surmised high temperature might improve the reaction rate TABLE 1.

To determine the optimal conditions for the reduction of á-amino acids, the reactions were carried out in reflux at different molar ratios of $AlCl_3$ to amino acid using L-Phenylalanine as the model substrate. The results are summarized in TABLE 2. As the molar ratio of $AlCl_3$:amino acid increases from 0.9:1 to 1.5:1, the yields of the chiral amino alcohol increase. There is no significant influence on the yield by using more equivalents of $AlCl_3$ relative to amino acid. It suggested that 1.4 equivalent of $AlCl_3$ is adequate to reduct the amino acids to the corresponding â-amino alcohol.

CONCLUSION

In summary, $KBH_4/AlCl_3$ is a more facile, efficient, convenient, reducing agent for the reduction of á-amino acids to the corresponding alcohols, and it also has features of good yields under mild conditions.

ACKNOWLEDGMENTS

We gratefully acknowledge Dr. Bao-Hua Chen, College of Chemistry and Environmental Science, Hebei University, Baoding, for his continuous support.

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