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Research Article

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A Reduction of Chiral Amino Acids Based on Current Method

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ABSTRACT

This paper aims to introduce a simple and convenient method for the industrial production of chiral amino alcohols. Based on the current reduction of chiral amino acids, this work can efficiently simplify the experimental procedure by using Li as reducing agent and $AlCl_3$ as auxiliary material to activate the carboxyl group of amino acids. In order to show the practicability of our method, L-phenylalanine and other several kinds of chiral amino acids were applied to this reduction, and through suitable condition setting, the yield of our tests reached 74.8~91.4%.

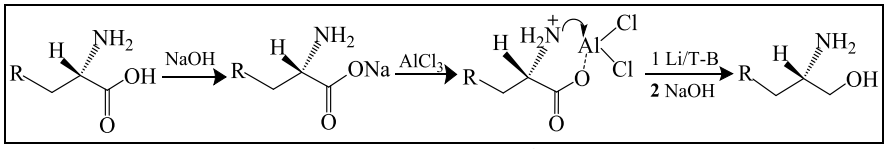
Keywords: Chiral aminos alcohol; Chiral amino acids; optimized work; Li; $AlCl_3$

INTRODUCTION

Chiral amino alcohols are a kind of important molecular compound with optical activity, diversified structures, and good selectivity [1]. They have been widely applied in the fields of materials, pharmaceutical, asymmetric synthesis, fine chemicals and so on [2-4]. Therefore, it has practical significance on the study of high efficiency, low cost and large scale preparation of chiral amino alcohols. Chiral amino alcohols are generally prepared by the reduction of α-amino acids and $LiAlH_4$, $NaBH_4$ or H_2 are commonly used reducing agents. For example, Dickman et al [5] had accomplished the reduction of valine to valinol by $LiAlH_4$, its yield was 73~75%. Quirk et al [6] had used Pd/C as catalyst to hydrogenate C=N double bond to prepare serinol and the yield reached 81-83%. Mariappan et al [7] had used $NaBH_4$/ I_2 to reduce eight kinds of amino acids, and the yield reached 80~98%. Kenso Soai et al [8] had reported using $NaBH_4/CH_3OH$ to reduce ester groups and also obtained a good yield: 88%~94%.

As regards those methods, metal-hydride compounds that represented by $LiAlH_4$ has a strong activity and can directly reduce carboxyl groups to alcohols. But they are expensive in price, cumbersome in preservation and high risk in large-scale application. Therefore, they are more suitable to laboratory application. Catalytic hydrogenation reaction is a green and efficient route for the preparation of chiral amino alcohols with broad industrial prospect. But generally, this reaction is under high pressure and high temperature, which means it has a higher demand for the equipments. Moreover, a certain kind of catalyst only matches several similar structures. Therefore, this method is relatively costly and inconvenient. Recently, researches on $NaBH_4$ associated with auxiliary agents such as $LiCl_4$ [9], H_2SO_4 [10], I_2, CH_3OH, DDC [11] (N,N'-dicyclohexylcarbodiimide) and so on, witch can extend its application and improve its reducing ability towards amino acids, have become a hotspot. But the operation of such reactions is cumbersome, and many by-products are also produced, it can increase the difficulty of their post-processing.

Compared with those methods above, our method is relatively simple and convenient. It is also suitable to the reduction of different kinds of amino acids and can be applied to large-scale industrial production. The preparation pathway is briefly showed in scheme 1, in this reduction, Li is used as reducing agent, $AlCl_3$ is used as auxiliary agent to activate the carboxyl group of amino acid and tert-butanol(Li/T-B) is used to donate H^+.



Scheme 1: The preparation pathway for amino alcohols

EXPERIMENTAL SECTION

Materials

Sodium hydroxide and L-phenylalanine were obtained from Evonik Degussa Specialty Chemicals Co. Ltd (GER), other chemical reagents such as tert.-butyl alcohol, aluminum chloride, lithium, tetrahydrofuran, ethyl acetate, etc, were obtained from Heowns Chemicals Co. Ltd (USA).

Preparation of sodium L-phenylalanine

Sodium hydroxide solution (32 mL, 0.01mol/mL) was poured into a 100 mL beaker, and then L-phenylalanine (50.00 g, 0.30mol) was slowly added in. The temperature was maintained at 60 °C with stirred for 20 min. After that, cooling the solution for crystallization, and then the crystals was filtered and dried to obtain product.

Preparation of L-phenylalaninol

$AlCl_3$ (1.80g, 13.48mmol) was added to anhydrous tetrahydrofuran (30 mL) and then Sodium L-phenylalanine (2.50g, 13.37mmol) was slowly added in. The temperature was maintained at 55 °C with stirring for 1 hr. The pH was maintained at 3~4. After that, Li chips (0.56g, 80.00mmol) and tert-butanol (10 mL) were separately added in. The temperature was maintained at 65 °C with stirring for another 1.5 hr. Then the solvent was removed and the remaining solid residue was dissolved in 10% NaOH solution (30 mL,) for 3 hr of hydrolysis at room temperature. After that, dilute HCl liquid (5 mol/L) was dropped in for the solution's acidification, and then the crude products were filtered, washed, dried and recrystallized from methanol. Finally 1.92 g product was obtained and the yield was 91.2%. m.p. is 93-94, ^{1}H NMR ($CDCl_3$) δ: 7.34 -7.18 (m, 5H, Ph*H*); 3.64 (dd, 1H, CH_2 OH), 3.36 (dd, 1H, CH_2 OH), 3.12,(m, 1H, H_2N C**H*), 2.80 (dd, 1H, CH_2 Ph), 2.53 (dd, 1H, CH_2 Ph), 1.64 (br, 3H, N$H_2$and O*H*), IR (KBr) ν: 3353, 3298, 3030, 2876, 2820, 1576, 1490, 1456, 1339, 1227, 1066 cm^{-1}.

RESULTS AND DISCUSSION

Application of this method

This method was applied to prepare L-phenylalaninol, D-phenylalaninol, L-phenylglycinol and other seven kinds of chiral amino alcohols, the recorded data are showed in table 1.

Table 1: Yield and physical properties of products

Entry	Products	Yield/ %	m.p.(°C)/ lit[12]	$[\alpha]_{20D}$/lit[12]
1	L-Phenylalaninol	91.2	93-94/ 92-95	-22 /-22 (c=1.2,1N HCl)
2	D-Phenylalaninol	91.4	93-95/ 93-95	+22 /+23 (c=1.2,1N HCl)
3	L-Phenylglycinol	89.5	74-76/ 74-76	+31/+31 (c=0.75,1N HCl)
4	D-Phenylglycinol	89.3	75-76/ 75-77	-32 /-32 (0.75,l M HC1)
5	L-Prolinol	86.6	74-76/ 73-76	+32/+31 (c=1,$C_6H_5CH_3$)
6	L-tert-Leucinol	85.8	32-34/ 32-34	+36+37 (c=1.5,EtOH)
7	L-Isoleucinol	87.2	29-30/ 28-30	+5.0/+4.9 (c=1.6,EtOH)
8	L-leucinol	87.5	197-200/ 197-200	+3.8/+3.7 (c=9,EtOH)
9	L-Valinol	79.4	27-30/ 29-30	+16/+17 (c=10,EtOH)
10	L-Methioninol	75.3	34-35/ 34-36	-12/-12 (c=1.4,EtOH)
11	L-Alaninol	74.8	174-175/ 171-174	-17/-16.5 (neat)

Table 1 has showed that the yield of our tests reached 75.3~91.4%, but there is an obvious gap between 11 and 2, the speculated reason can be summarized as the following points. First, the products' water-solubility is a key factor. For example, the water-solubility of 9, 10, or 11 with simple structure is stranger than 2, witch can increase the difficulty of their extraction. Second, the electronic effect and steric effect also have influence on the yield.

For example, products such as 1, 2 or 3 have phenyl group with electron-withdrawing effect, it can weaken the electron cloud density of carboxyl groups and facilitate their preparation. But compared with 1, the steric effect of 2 or 3 is stranger, so their yield is a little lower. On the other hand, the yield of 1 is only slightly lower than 2, it proves the molecular configuration has little effect on the reduction.

The influences of reactants ratio, reaction temperature and time are also of vital importance. Around them, we had done a lot of researches. Theoretically, the reduction of 1 mole of amino acid needs 4 mole of Li, but in the real tests, the amount of Li needs to be excessive. The effect of reactants ratio on the yield is showed in figure 1 (other conditions are optimum).

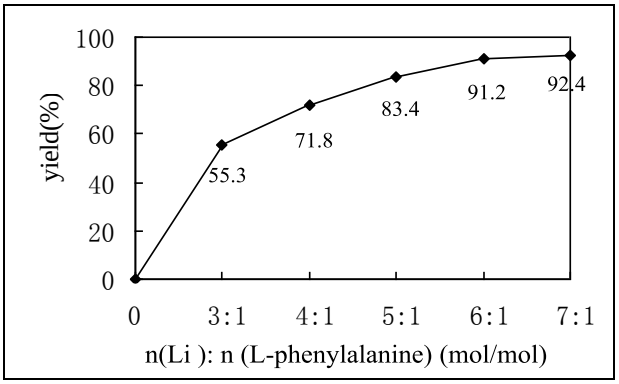


Figure 1: Effect of reactants ratio on the yield

Figure 1 has shown that the yield of L-phenylalaninol is gradually increased when the material ratio of Li and L-phenylalanine is raised from 3: 1 to 7: 1 (mol/mol), but there is unobvious increase between 6:1 and 7:1 (mol/mol). Considering the material consumption, this method set reactants ratio to 6: 1 (mol/mol). The effect of time and temperature is showed in figure 2 (other conditions are optimum).

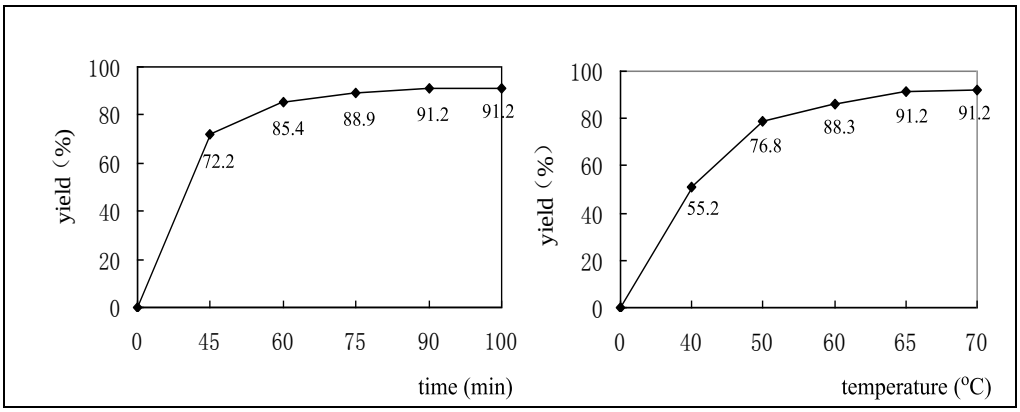


Figure 2: Effect of time and temperature on the yield

Figure 2 has shown that the highest yield 91.2% can be reached under the condition of time is 90 min and temperature is 65 °C, witch means this reduction is relatively fast and saving energy.

The condition setting of $AlCl_3$ chelated with amino acids was also researched. As chelate reaction is reversible and different material ratios form different structure [13], the material ratio of $AlCl_3$ and L-Phenylalanine was set to 1: 1, so that L- phenylalanine was fully involved in coordination. Dissolved Al^{3+} starts to precipitate at pH 3.3 and completely precipitates at pH 5.4, so the pH of chelate reaction was maintained at 3-4. The effect of time and temperature is showed in figure 3.

Figure 3 has showed that the reaction had reversed when temperature was raised to 60 ℃, and after 45 minutes, time had little effect on the yield.

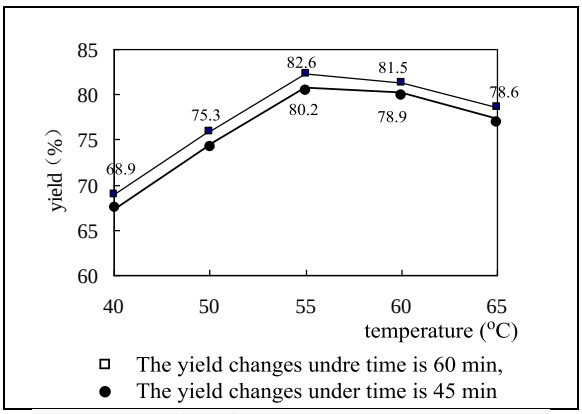
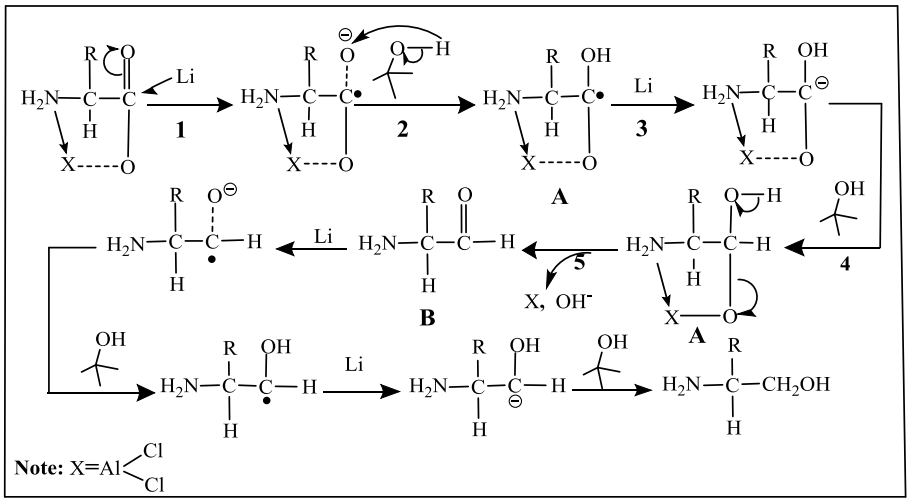


Figure 3: The effect of time and temperature on the yield

Principle and material selection

The principle [14-16] of this method is briefly showed in scheme 2. Under the condition of tert-butanol donating H^+, the carbon atom of carbonyl group is successively attacked by two electrons from Li (step 1 and step 3) and then formed unstable intermediate A. In step 5, A takes off the groups in a form of OH^- and X through electron transfer to form C, and then C repeated the steps of 1-4 to form amino alcohols.

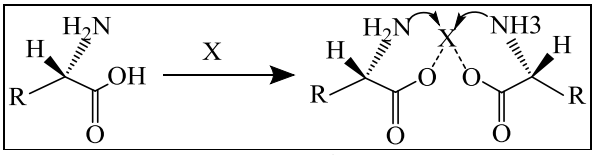


Scheme 2: Principle of this method

According to the classic Bouveault-blanc reduction, Na associated ethanol (H^+ donor) can reduce esters to alcohols. Although its yield is relatively lower, it provides a theoretical basis for our selection of Li as reducing agent. In the practical application, Li also has a certain reducing power, and compared with Na or $LiAlH_4$, its reaction is milder and easier to be controlled. Moreover, its by-products is fewer and post-processing is convenient. But using Li alone as reducing agent can not directly reduce amino acids, a kind of auxiliary agents should be added to activate the carboxyl group of amino acids. For its selection, our main consideration is the price and efficiency. Then $AlCl_3$ was found more suitable, because it can chelate with amino acid and then activate the carboxyl group through its electron-withdrawing effect [17-18]. It also has little influence on the reducing agent Li. As regarded the H^+ donor, alcohol is a good choice, but low carbon alcohols such as ethanol or propanol can directly react with Li or $AlCl_3$. So tert-butanol was chosen to weaken this influence.

Detailed research on the chelate reaction

In general, soluble metal ion with bonding orbitals that lack of electronics can react with amino acid and then formed compound with multiple ring structure [19]. The illustration is showed in scheme 3.



Scheme 3: Illustration of chelate reaction

In this method, the sodium salt of amino acid was first prepared. The reason was to make the hydroxyl group ionization and facilitate its chelating with Al^{3+}. We speculated that through the electron-withdrawing effect and steric effect, the chelated Al^{3+} can weaken the bond energy of carbonyl group and then facilitate it to be reduced. In order to demonstrate our speculation, L- phenylalanine was used as example to chelate with $AlCl_3$, The recorded infrared data of its carboxyl and amino group are showed in table 2.

Table 2: Infrared data of carboxyl and amino group

	v_s(N-H)	v_{as}(N-H)	v_s(-COO$^-$)	v_{as}(-COO$^-$)
v_1	3284	3359	1406	1575
v_2	3257	3320	1417	1610

v1: wavenumber of sodium L- phenylalanine;
v2: wavenumber of the chelate.

Table 2 has showed that two absorption peaks of N-H move to low wavenumber (from 3284, 3359 to 3257, 3320) and two absorption peaks of –COO$^-$ move to high wavenumber (from 1406, 1575 to 1417, 1610). It proves that the amino and carboxyl group have been involved in the chelate reaction [20]. The changes of carboxyl's infrared data also prove that the electron cloud density of C=O is weakened and its bonds energy is decreased.

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