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Transition Metal Compound Mediated Reduction of α -Amino Acids to 1,2-Amino Alcohols with NaBH_4 in Water

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A new efficient and cost-effective method for the preparation of 1,2-amino alcohols is described. The reactions of amino acids with NaBH_4 in the presence of NiCl_2 or MoO_3 in water give 1,2-amino alcohols in high yield. When optically pure amino acids were used, optically pure 1,2-amino alcohols were obtained.

Introduction

The chiral 1,2-amino alcohols are important compounds, because a large number of natural products contain the amino alcohol functionality and many amino alcohol derivatives have chemotherapeutic properties. They also have applications especially as chiral auxiliaries for different asymmetric synthesis reactions¹. 1,2-Amino alcohols can be prepared from readily available amino acids. Reduction of amino acids to form amino alcohols has been reported recently. One approach uses a sodium borohydride-sulfuric acid system², while another employs NaBH_4 -iodine³. Other reagents have also been used for the reduction of amino acids, such as lithium aluminum hydride⁴, borane-methyl sulfide in the presence of boron trifluoride etherate⁵, and lithium borohydride in the presence of trimethylsilyl chloride⁶.

Sodium borohydride is a mild reducing agent with high selectivity. The combination of sodium borohydride with cobalt, nickel, iridium, osmium, copper, platinum, titanium, and rhodium halides has been employed to reduce functional groups, which are inert to sodium borohydride alone⁷.

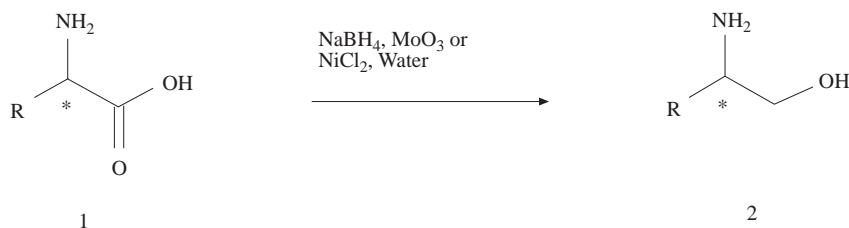
Experimental

General method for the preparation of 1,2-amino alcohols:

To a mixture of α -amino acid (30 mmol) and transition metal compound (45 mmol, 1.5 equivalent) in water (100 mL) NaBH_4 (300 mmol, 10 equivalent) (exothermic reaction, reflux condenser is necessary) was carefully added at room temperature (evt. cooling). An alternative procedure is the addition of transition metal compound to the mixture of amino acid and NaBH_4 in water. This method sometimes gave a better yield. The resulting dark mixture was stirred at ambient temperature for 6-10 h (checked by TLC; Silical

Gel, EtOAc:Hexane:MeOH 1:1:1). The residue was treated with aqueous KOH (20%, 20 mL) and extracted several times with dichloromethane. The aqueous layer was saturated with NaCl and extracted again with dichloromethane. The combined organic layers were washed with water and again with brine, before being dried over MgSO₄. After filtration and evaporation of solvent, the 1,2-amino alcohols were obtained as an oil or solid. Further purification was achieved by distillation under vacuum or by recrystallization.

Results and Discussion



Scheme 1

We have previously reported that treatment of hydroxyiminophosphonates with sodium borohydride in the presence of MoO₃ or NiCl₂ afforded the aminophosphonic acids in good yield⁸. In this study we would like to report the selective reduction of α -amino acids with the same transition metal compounds.

As shown in Scheme 1, the reduction of α -amino acids with sodium borohydride in the presence of NiCl₂ or MoO₃ at ambient temperature in water gave the corresponding 1,2-amino alcohols in high yield. The reduction is carried out by adding NiCl₂ or MoO₃ to the mixture of NaBH₄ and amino acid in water. This reaction step is exothermic and sometimes cooling is necessary. The same reaction can also be achieved by adding NaBH₄ to the solution of amino acid containing one of the above transition metal compounds. Different amino acids were used for this reduction with different functional groups and corresponding 1,2-amino alcohols were obtained (Table). As expected, the optical purity of 1,2-amino alcohols, determined from the optical rotation values, were the same as the starting material. By all reduction reactions NaBH₄ was used in excess, and the ratio for the best yield was: substrate/ NiCl₂ or MoO₃/ NaBH₄ 1/1.5/10. Decreasing the amount of NaBH₄ decreased the yield of the reaction rapidly.

The reaction of NaBH₄ with NiCl₂ and MoO₃ is exothermic and deposits a black granular precipitate, which is referred as metal boride in the literature^{7,9}. This precipitate was collected by filtration. After the excess borohydride has hydrolyzed, the water was decanted and black granules were washed with absolute ethanol. The reduction of amino acids in the presence of NaBH₄ was also attempted with this solid material instead of NiCl₂ and MoO₃, but no reaction took place. The same black granules were also used for the hydrogenation of amino acids in a Parr hydrogenation apparatus but this experiment also gave no product. After all of these experimental observations, we think that the mechanism involves the transition metal assisted hydride reduction, while the corresponding borides are formed.

Table 1. Reduction of Amino Acids with NaBH₄/NiCl₂ and NaBH₄/MoO₃ in water^a

Amino Acid	Amino alcohol Yield (%) ^b		mp (bp/mm Hg) ^{2,10}
	MoO ₃	NiCl ₂	
L-Proline	78	81	74-76 °C/2
L-Valine	73	78	(100-102 °C/25)
L-Phenylalanine	82	83	92-94 °C
L-Alanine	73	77	(172-174 °C)
DL-Phenylglycine	83	81	74-77°C
L-tert.Leucine	77	76	(102-104 °C/18)
DL-Methionine	71	78	(134-138 °C/8)

a) The spectroscopic data of the amino alcohols are in agreement with the published data^{2,10}. b) The reaction was monitored by TLC until no more starting material was present. This was consistent with 100% conversion of reactant to the product. Lower experimental yields were due to the loss of some material during the isolation process.

It can be concluded that the NaBH₄-MoO₃ and NiCl₂ system provides a useful and simple synthetic route under mild conditions for the preparation of 1,2-amino alcohols from α -amino acids. Large scale preparation is also possible.

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