

## Mild Reduction of Carboxylic Acids to Alcohols Using Cyanuric Chloride and Sodium Borohydride

Massimo Falorni,\* Andrea Porcheddu and Maurizio Taddei

Dipartimento di Chimica, Università di Sassari, Via Vienna 2, 07100 Sassari, Italy

Received 26 January 1999; revised 7 April 1999; accepted 12 April 1999

### Abstract

Several carboxylic acids, including *N*-Boc, *N*-Cbz and *N*-Fmoc amino acids were reduced to the corresponding alcohols by activation of the carboxy function with cyanuric chloride and *N*-methylmorpholine followed by reduction with aqueous sodium borohydride.

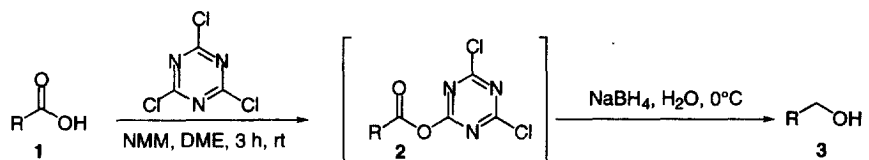
© 1999 Elsevier Science Ltd. All rights reserved.

**Keywords:** Reduction, Carboxylic acids, Alcohols, Amino acids.

The selective reduction of carboxylic acids to alcohols is still an important task for organic chemists. Several reagents will carry out this reaction, for example, lithium aluminium hydride, boranes or modified sodium borohydride [1]. Some of these reagents suffer from limitations such as the use of anhydrous solvents, hazards in handling the reducing agent or incompatibility with other functional or protective groups present in the molecule. This last drawback may occur in the reduction of protected amino acids, as the Boc protecting group is labile in the presence of NaBH<sub>4</sub>/acids and the Cbz or the Fmoc protecting group may be cleaved with LiAlH<sub>4</sub> or BH<sub>3</sub>. For amino acid derivatives a possible alternative is to reduce the unprotected amino acid to amino alcohol followed by protection of the amino group [2]. When this protocol is not possible, the carboxyl group can be activated using the mixed carbonic anhydride approach followed by reduction with NaBH<sub>4</sub> [3]. Although this last procedure is very efficient, we sometimes noticed the formation of different amounts of the ester derived from decarboxylation of the intermediate carbonic anhydride that occurred before the reduction step. The ester is not reduced by NaBH<sub>4</sub> in water and must be separated from the desired alcohol by column chromatography. The chemoselective reduction of carboxylic acids to alcohols by activation of the carboxyl group with BOP followed by reduction with NaBH<sub>4</sub> was described recently [4]. Although very simple, this procedure cannot be reasonably carried out on large scale due to the high cost of the BOP reagent. [5]

We report here that carboxylic acids can be activated with cyanuric chloride [5] and subsequently reduced to the corresponding alcohol with NaBH<sub>4</sub> in water.

A typical procedure, applied to the reduction of *N*-Cbz-proline, is as follows: to a solution of cyanuric chloride (0.92 g, 5 mmol) dissolved in DME (30 mL, commercial grade) *N*-methylmorpholine (0.55 mL, 5 mmol) was added at room temperature under stirring. A white suspension was formed and to this mixture a solution *N*-Cbz-proline (1.24 g, 5 mmol) in 10 mL of DME was added. After 3 h at room temperature the mixture was filtered (Buchner funnel). The flask was cooled to 0°C and NaBH<sub>4</sub> (0.28g, 7.5 mmol) dissolved in water (15 mL) was added (attention: evolution of gas was observed during the addition). The mixture was stirred for additional 5 min at 0°C and diethyl ether was added. The solution was acidified (HCl 10% or KHSO<sub>4</sub> can be used depending on the nature of the substrate). The organic layer was separated and subsequently washed with a solution of Na<sub>2</sub>CO<sub>3</sub> 10% and brine. After drying over anhydrous Na<sub>2</sub>SO<sub>4</sub> the solvent was evaporated to give 1.04 g of pure Cbz-Prolinol (89% yield, [α]<sub>D</sub><sup>25</sup> = -42.5 (c = 2, CDCl<sub>3</sub>), lit [α]<sub>D</sub><sup>25</sup> = -41.4 (c = 2.2 CDCl<sub>3</sub>). [6]

Table: Reduction of carboxylic acids with cyanuric chloride, NMM and NaBH<sub>4</sub>

Carboxylic acid	Yield of alcohol <sup>a</sup>	Carboxylic acid	Yield of alcohol <sup>a</sup>
R = PhCH <sub>2</sub> CH <sub>2</sub> -	92%	Cbz-Pro-OH	89%
R = Ph <sub>2</sub> CH-	88%	Boc-Ala-OH	90%
R = o-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -	97%	Boc-Asp(OBn)-OH	73%
R = 3,4,5-(MeO) <sub>3</sub> C <sub>6</sub> H <sub>2</sub> -	77%	Boc-Glu-OBn	98%
R = BrCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -	76%	Fmoc-Phe-OH	75%
R = PhCH=CH-	93% <sup>b</sup>	Fmoc-Val-OH	85%

a) Yields refer to isolated and fully characterized products.

b) Yield refers to a 80 : 20 mixture of unsaturated : saturated compounds.

As described in the table, this procedure is particularly suitable for protected amino acids; Boc, Cbz and Fmoc protective groups are stable under these conditions. The different carboxylic groups of aspartic and glutamic acids can be reduced in good yield without affecting the other ester function. The optical purity of the alcohols derived from amino acids was established by comparing the optical rotation values with those reported in the literature. The occurrence of racemisation was never observed. [7]

In the case of reduction of conjugated acids as cinnamic or crotonic acids the major product was the expected allylic alcohol together with 15-20% of the saturated alcohol arising from the unavoidable reduction of the product with NaBH<sub>4</sub> in alkaline medium. Further attempts to optimise this procedure or to drive the reduction to the formation of aldehydes are currently underway and will be reported in due course.

**Acknowledgements.** This work was financially supported by MURST (Rome) within the project "Chimica dei Composti Organici di Interesse Biologico" Es. Fin. 1997.

#### References and Notes.

- [1] Larock, R.C. *Comprehensive Organic Transformations*, VCH: New York, 1989; 548.
- [2] Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 5517
- [3] Kokotos, G. *Synthesis*, **1990**, 299. Rodriguez, M.; Llinares, M.; Doulut, S.; Heitz, A.; Martinez, J. *Tetrahedron Lett.* **1991**, *32*, 923.
- [4] McGeary, R.P. *Tetrahedron Lett.* **1998**, *39*, 3319.
- [5] Cyanuric chloride, price about 5.5 Euro per mol. BOP reagent, price about 19000 Euro per mol. Source: The Aldrich catalogue, 1999-2000, prices in Italian Lira.
- [6] St-Denis, Y.; Chan, T-H. *J. Org. Chem.* **1992**, *57*, 3078
- [7] The absence of racemisation suggested that the intermediate **2** is formed instead of the corresponding acyl chloride as reported by: Venkataram, K.; Wagle, D.R.; *Tetrahedron Lett.* **1979**, *32*, 3037.