



Reduction of carboxylic acids to alcohols using phosphonitrilic chloride and sodium borohydride

Jitendra S. Pulle*¹, Ashok D. Sagar², Sanjeev M. Reddy³ and Manjusha V. Yadav⁴

¹Department of Chemistry, S. G. B. College, Purna (Jn.), Dist. Parbhani (M.S.), India

²School of Chemical Sciences, S. R. T. M. University, Nanded, India

³Department of Chemistry, G. M. V. Kotgyal, Dist. Nanded (M.S.) India

⁴Department of Chemistry, Government Polytechnique College, Nanded (M.S.) India

ABSTRACT

The aliphatic carboxylic acids were reduced selectively to corresponding alcohols by activation with phosphonitrilic chloride (PNT) and subsequently reduced using sodium borohydride as a reducing agent under mild conditions.

Key words: Phosphonitrilic chloride, sodium borohydride, reduction, carboxylic acids, alcohols.

INTRODUCTION

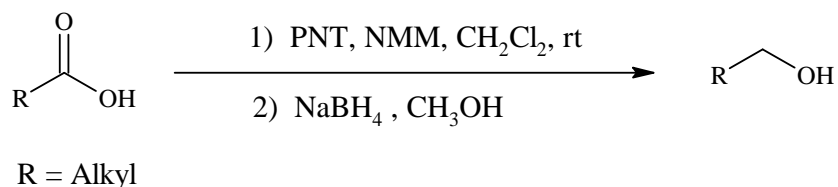
Sodium borohydride is the most widely used reducing agent [1] discovered by H. I. Schlesinger and H. C. Brown [2]. It brought great change in the methods for reducing the functional groups. It is soluble in water and possesses unique properties in organic synthesis. It was used in the stereoselective reduction reactions due to its usefulness as a hydride reducing agent for both chemo- and diastereo-selectivity [3]. It was used as a reducing agent in which borohydride anion species is responsible for its reductive properties. The advantage of using sodium borohydride as reducing agents is that the reducing properties of borohydride were secured without releasing sodium and borate into the system. Sodium borohydride was used as reducing agent for the simple chemo-selective reduction reactions of aldehydes and ketones to alcohols [4]. It has very low moisture sensitivity therefore it is better than lithium aluminium hydride and lithium borohydride [2,4a,5]. It was extensively used as a reducing agent in alcoholic solvents [6]. Sodium borohydride / Carboxylic acids system is a versatile and efficient reducing system [7]. Carbonyl compounds were reduced under solvent-free conditions using sodium borohydride and HSBM [8]. Reductive amination of carbonyl compounds were carried out by the reagents such as CF₃COOH [9], Mg(ClO₄) [10], aq. sulfuric acid [11], Ti(OiPr)₄[12], Nickel chloride [13].

Carboxylic acid derivatives such as nitriles, esters, lactones and amides could not be reduced individually by sodium borohydride even though it is less expensive, safe and more convenient [14]. In order to increase the reactivity of sodium borohydride, various additives [14, 15] were used. In reduction reactions sodium borohydride was used as reducing agent along with additives such as Sulfur [16], methanesulfonic acid and TiCl₄ [17], calcium chloride [18], stannous chloride [19], zirconium chloride [20], Me₃SiCl [21], CeCl₃ [22], (L)-tartaric acid [23], iodine [24], manganese chloride [25], zinc chloride [26], Et₃SeBr₂ [27], BH₃·Me₂S [28], cyanuric chloride [29], 3,4,5-trifluorophenylboronic acid [30], MoCl₅[31], BF₃·Et₂O [32], titanyl acetylacetonate [33] LiClO₄ [34], guanidine hydrochloride[35], HOBt/EDC [36] .

In search and development of an efficient reagent for the activation of carboxylic acids we studied phosphonitrilic chloride trimer (PNT) as activator. However sodium borohydride was found to be useful reducing agents for the conversion of carboxylic acids to alcohols. PNT containing six chloride atoms present over the phosphorous atoms of the stable phosphazine ring, which shows more reactivity towards nucleophiles [37]. Therefore, PNT was used for

the activation of carboxylic acids similar to cyanuric chloride. It could activate six equivalents of carboxylic acids which is twice than that of cyanuric chloride. Importantly PNT is less moisture sensitive and non irritating compound, also it is easy to handle. Therefore, we investigated the activation of carboxylic acids with PNT and subsequent reduction to alcohols by using sodium borohydride under mild conditions.

In the present work, aliphatic carboxylic acids were selectively reduced to corresponding alcohols using PNT as activator together with N- methyl morpholine (NMM) and NaBH₄ as reducing agent (Scheme 1).



Scheme 1

MATERIALS AND METHODS

To a solution of PNT (0.25 mmol) in dichloromethane (30 ml) NMM (1.5 mmol) was added at room temperature with stirring. To this solution, carboxylic acid (1.5 mmol) in dichloromethane (10 ml) was added. After stirring for 3 hrs., NaBH₄ (7.5 mmol) in methanol (15 ml) was added and continued the stirring of mixture for about 1-2 hours at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, dichloromethane and methanol were evaporated under reduced pressure. Diethyl ether was added to this flask. The solution was acidified with HCl (10 %). The organic layer was separated, washed with sodium bicarbonate (10 %) and brine 10 % (2 x 10 ml) and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give corresponding alcohol in pure form.

RESULTS AND DISCUSSION

New method was developed for the reduction of carboxylic acids to corresponding alcohols in good to excellent yields (Table 1). Initially, we utilized PNT-NaBH₄ system (Scheme 1) and found that PNT activates double equivalents of carboxylic acid compared to cyanuric chloride. Working with PNT is easier than moisture sensitive and irritating cyanuric chloride. The system reduces only aliphatic carboxylic acids without reducing the aromatic carboxylic acids (entries 13 to 15). Similar to cyanuric chloride, yields of unsaturated carboxylic alcohol product was moderate (entry 8). This could be due to reduction of olefinic double bond together with carboxylic acids of the substrates because of NaBH₄ which is strong reducing agent.

Table 1: Reduction of carboxylic acids using PNT/NaBH₄

Entry	Carboxylic acids	Alcohols	PNT/ NaBH ₄ Yield (%)	M.P./B.P. [°C] [Lit] [38]
1			90	48-49 [49]
2			88	217-219 [219]
3			90	145-146 [146]
4			88	96-97 [97-98]
5			90	233-235 [235]

6			86	57-58 [56-58]
7			89	229-231 [232]
8			90	248-249 [250]
9		----	----	----
10		----	----	----
11			78	91 [92-94]
12			81	88 [88-91]
13			89	217-218 [219]
14			90	156-157 [158]
15			87	57-58 [59]

CONCLUSION

Both PNT - NaBH₄ reduces aliphatic carboxylic acids in good to excellent yields at room temperature. PNT activates double equivalent of carboxylic acids compared to cyanuric chloride thereby reducing half equivalent amount of catalyst loading to the reaction. NaBH₄ together with PNT reduces olefinic double bonds of carboxylic acid.

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