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Efficient method for the synthesis of 3-pyridyl methanol from nicotinic acid using sodium borohydride-methanol system

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ABSTRACT

Nicotinic acid is esterified by using methanol as a solvent in catalytic amount of concentrated Sulfuric acid, to get methyl nicotinate, which was subsequently reduced with $\text{NaBH}_4\text{-MeOH}$ system to 3-pyridyl methanol in high yields.

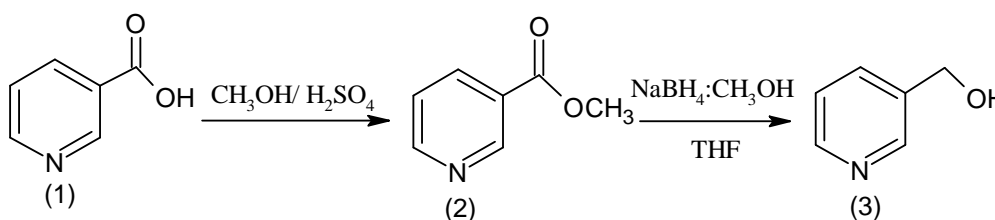
Keywords: Methyl nicotinate, 3-Pyridyl methanol, Sodium borohydride, Reduction.

INTRODUCTION

The sodium borohydride is relatively mild reducing agent and specific for the reduction of carbonyl group in aldehydes and ketones, while the lithium aluminium hydride is an exceedingly powerful reducing reagent as it attacks all reducible groups. The reducing capacity of the borohydride is markedly affected in the presence of the metal ion. Thus the sodium borohydride reduces typical esters, such as ethyl acetate and ethyl benzoate [1]. The reduction of the esters to primary alcohols using large excess of sodium borohydride in methanol has been reported in literature by Schenker [2] on his excellent review. It is evident that the esters are not resistant for the reduction by sodium borohydride, but the rate of reduction is much slower than aldehydes and ketones. Methyl nicotinate has been reduced in high yields to the corresponding alcohols by using 20-fold excess of sodium borohydride in methanol. The ketones or aldehydes are reduced in the presence of an ester function, to avoid large excess of borohydride and elevated temperatures to control partial reduction of ester [3]. However, due to its relatively cheaper cost and ease of handling, modification to augment its reducing power has never stopped. This includes changing the reaction conditions such as varying the solvent, increasing its amount, adding additives or even using catalysts. For instance, sodium borohydride methanol system can reduce ester provided that the reaction was done under refluxing THF. There have been few

reports on the reduction of α -keto esters and β -keto esters using sodium borohydride in ethanol solvent. The yields are quite low and the reaction time is sometimes too long [4]. Usually, when the reactions with NaBH_4 are safe, inexpensive and can be done under milder conditions, it is not common to use NaBH_4 itself for reduction of esters, due to low reactivity towards esters, additives which enhance the activity of NaBH_4 . For example, addition of iodine to NaBH_4 in THF provides $\text{BH}_3\text{-THF}$, which is useful for hydroborations, reduction of esters and various others functional groups, aromatic ethyl, isopropyl and benzyl esters into the corresponding alcohol using $\text{NaBH}_4\text{-MeOH}$ system [5]. Considering this context, the aim of the present research methodology is to describe a simple reduction of aromatic ester into the corresponding alcohol using $\text{NaBH}_4\text{-MeOH}$ system. This methodology could also be a good procedure to employ in an industrial process [6].

Here after esterification, methyl nicotinate is reduced to corresponding alcohol using reducing agent $\text{NaBH}_4\text{-MeOH}$ system in refluxed THF (**Scheme-1**).



Scheme 1

MATERIALS AND METHODS

Further melting points were, taken by an open capillary method. Compounds were analyzed for their purity by TLC. Structures of the synthesized compounds have been confirmed on the basis of FT-IR (Perkin Elmer spectrum one) and GCMS (Shimadzu GC-2010) spectral analysis.

Methyl nicotinate: The solution of 12.30 gm, 0.1 mole Nicotinic acid in 30 ml methanol, to which 5 ml conc. H_2SO_4 was added and the reaction mixture refluxed for 16 h. After the completion of the reaction, mixture was cooled and neutralized with NaHCO_3 and the separated mass was extracted in Chloroform. Chloroform is removed under reduced pressure to get white crystalline compound, yield 80%, m.p. 38°C . IR (KBr) ν_{max} : 2955, 1729, 1591 cm^{-1} . GCMS (m/z): 137, 119, 106, 93, 78, 59, 51ppm.

3-Pyridyl methanol: The mixture of methyl nicotinate 13.7 gm, 0.1 mole and finely powdered sodium borohydride 75.66 gm, 2.0 mole was suspended in THF followed by addition of 8 ml. of methanol, the same reaction mixture was refluxed for 24 h. After completion of the reaction, the mixture was cooled to room temperature and quenched with sat. aq. NH_4Cl 30 ml. with continuous stirring for 15 h. The organic layer was separated out and the aqueous layer extracted with ethyl acetate twice (20 ml.). The combined extracts and organic phase were dried over MgSO_4 and concentrated to give desired alcohol purified further by recrystallized from ethyl acetate, yield 70%, (Thick oil). IR (KBr) ν_{max} : 3294, 2933, 2845, 1564, 1421 cm^{-1} . GCMS (m/z): 108, 91, 80, 65, 53, 40 ppm.

CONCLUSION

In conclusion, we developed an inexpensive, simple, safe and general protocol for the synthesis of 3- pyridyl methanol from nicotinic acid via esterification process to one-pot reduction of aromatic ester using NaBH₄-MeOH system in THF.

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