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Piperidine Promoted Regioselective Synthesis of α, β-unsaturated Aldehydes

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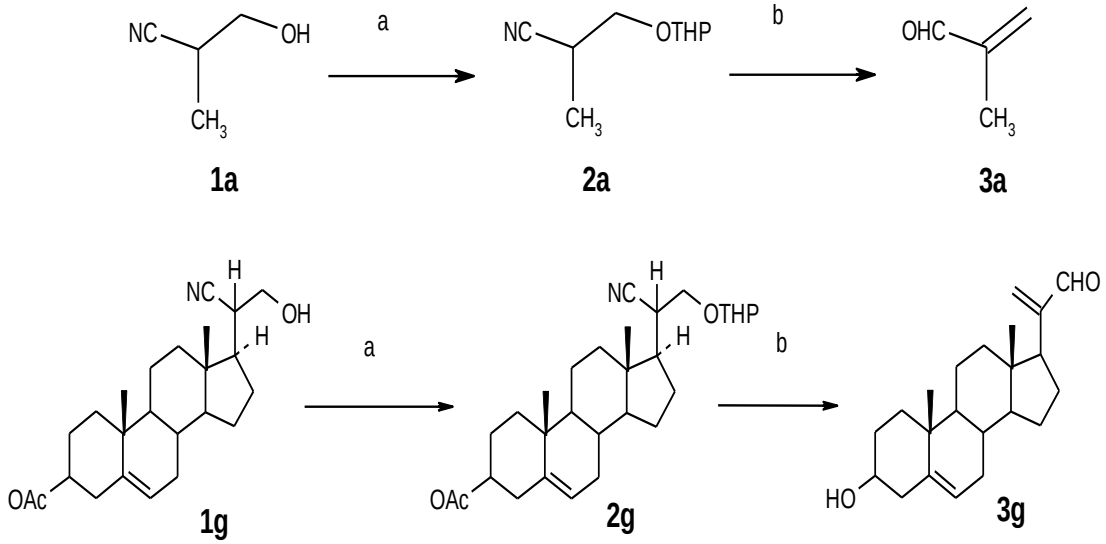
ABSTRACT
An efficient, facile and regioselective synthesis of α,β-unsaturated aldehydes from β-hydroxynitriles is reported. The reaction is carried out using DIBAL-H and promoted by piperidine under dry conditions at a temperature of -78 °C and can be described as a concomitant reduction-elimination reaction. The same reaction if carried out in the absence of piperidine gives mainly the uneliminated reduction product. The products formed are of immense importance as synthons in a large number of chemical reactions and biological processes.

Keywords: α,β-unsaturated aldehydes, metal hydrides, DIBAL-H, β-hydroxynitriles.

1. INTRODUCTION
Aldehydes in general and α,β-unsaturated aldehydes in particular are versatile substrates for the synthesis of a large number of molecules. Various methods have been used for the synthesis of the synthetically valuable α,β-unsaturated aldehydes. These methods include the reduction of nitriles, palladium catalysed dehydrosilylation of silyl-enol ethers, the Wittig reaction etc[1-2].

Isobutylaluminium alkyls are the versatile reagents mainly useful for reduction transformations. The varieties of these alkyls mainly include the diisobutylaluminium alkyl hydride (DIBAL-H) besides the less common diisobutylaluminium butylated oxy toluene (DIBAL-BOT) and the triisobutylaluminium (TIBAL). In comparison to metal hydride reducing agents, these catalysts offer various advantages for their use at the commercial scale. These organometallic catalysts offer conveniences in handling and stoichiometric additions besides offering stereo selectivity in some applications[3-5].

DIBAL-H is a versatile and unique organometallic hydride used for the reduction and preparation of pharmaceuticals and a large number of other laboratory chemicals. DIBAL-H has replaced most of the metal hydrides including $LiAlH_4$ and $NaBH_4$ on the commercial scale[6-8]. This can be attributed to the economic advantage, higher selectivity, cleaner reductions and high yields of the products. DIBAL-H being a liquid, unlike other metal hydride reducing agents, is miscible in most of the solvents and can be used for the reduction of a variety of substrates. Being easily oxidisable in the air, DIBAL-H reactions are easily worked up. It is an electrophilic reducing agent, usually employed in selective reductions of esters or nitriles to aldehydes; lactones to lactols; α,β-unsaturated carbonyl compounds to allylic alcohols, at low temperatures (-78°C)[6-9]. DIBAL-H reduces carbonyl or nitrile groups selectively in presence of double bonds, halide groups, ethers, nitro groups etc. Keeping all these things into consideration, we, in continuation of our research program towards use of organometallic reagents for the synthesis of various useful products[12-14], herein report the concomitant synthesis of α,β-unsaturated aldehydes from β-hydroxynitriles using DIBAL-H as an organometallic reductant under selective conditions.



Scheme 1: Concomitant conversion of β-hydroxynitriles to α,β-unsaturated aldehydes.a, DHP/p-TSA/DCM (95%); b, DIBAL neat/Toluene/-78 °C (80%) /Piperidine

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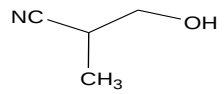
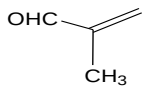
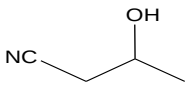
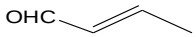
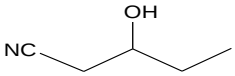
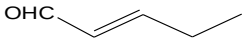
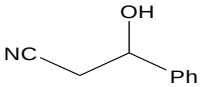
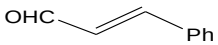
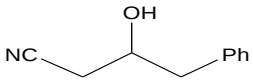
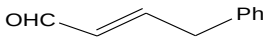
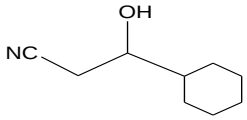
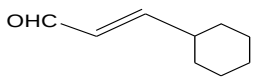
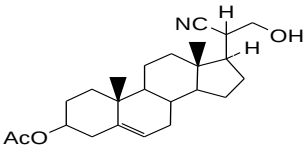
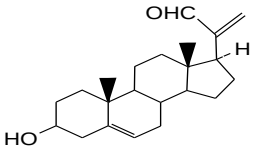
2. RESULTS AND DISCUSSION

Keeping in view the importance of α,β-unsaturated aldehydes as versatile precursors for the synthesis of huge number of useful compounds into consideration, we, in continuation of our interest in the development of novel methodologies using organometallic catalysts[12-14], herein report a facile synthesis of the α,β-unsaturated aldehydes by using DIBAL-H as the reducing agent in the presence of piperidine as the promoter for concomitant reduction-elimination reaction. β-hydroxynitriles were commercially obtained and the pregnenolone based β-hydroxynitrile was obtained through knoevenegal reaction of pregnenolone using well known synthetic strategy[15-16]. Though there are some methods already reported for the synthesis of various such steroidal analogs[17], our method differs in the strategy employed and the selectivity of the elimination product. The synthesis of steroid based α,β-unsaturated aldehyde **(3g)** was reported by us in a previous communication[18], which led to the synthesis of various such analogs as reported in this communication. It is very pertinent to mention here that when the carbon bearing the nitrile group was primary in terms of having two hydrogens, the yield of the resulting α,β-unsaturated aldehyde was quite insignificant. The reaction was carried out by first protecting the hydroxyl group at the β-position with DHP in dichloromethane using catalytic amounts of *p*-toluene-sulfonic acid. The DHP protected nitrile was then treated with DIBAL-H in dry toluene followed by 2 Mol% piperidine at a temperature of -78^{o}C. A very interesting situation was observed in the workup of the reaction. If the reaction time with DIBAL-H and piperidine was prolonged to 1 hr followed by treatment with methanol and subsequent workup, the main product was the α,β-unsaturated aldehyde. If however the reaction mixture was exposed to DIBAL-H for shorter periods (less than 10 min.) and not treated with piperidine after 10 min., the main product obtained was the corresponding β-hydroxy aldehyde. The reaction mixture was allowed to stand for 2 hrs after workup and then filtered through ceilite to get a crude gummy mass which when chromatographed over silica gel using Hexane:Ethylacetate, yielded the α,β-unsaturated aldehyde as the main product (>70%).

3. CONCLUSION

In conclusion we have successfully demonstrated here, the facile and unprecedented synthesis of industrially and biologically important α,β-unsaturated aldehydes through concomitant reuction/elimination of β-hydroxynitriles. The above reduction/elimination reaction was found to be general with regard to various β-hydroxynitriles.

Table-1: DIBAL-H catalyzed concomitant synthesis of α,β-unsaturated aldehydes

Entry	beta-hydroxynitriles	alpha-beta-unsaturated aldehydes [a]	Yield(%)
a			78
b			73
c			70
d			68
e			69
f			70
g			62

a. All compounds were characterized by ^{1}HNMR, IR 13C and Mass spectrometry in CDCI3

4. EXPERIMENTAL

4.1 *General*

Melting points were recorded on Buchi Melting point apparatus D-545; IR spectra (KBr discs) were recorded on Bruker Vector 22 instrument. NMR spectra were recorded on Bruker DPX200 instrument in CDCl3 with TMS as internal standard for protons and solvent signals as internal standard for carbon spectra. Chemical shift values were mentioned in δ (ppm) and coupling constants are given in Hz. Mass spectra were recorded on EIMS (Shimadzu) and ESI-esquire 3000 Bruker Daltonics instrument. The progress of all reactions was monitored by TLC on 2x5cm pre-coated silica gel 60 F254 plates of thickness of 0.25mm (Merck). The chromatograms were visualized under UV 254-366 nm and iodine.

4.2 *General procedure for the preparation of 3-(5,6-dihydro-4H-pyran-2-yloxy)-2-methylpropanenitrile (2a)*

3-hydroxy-2-methylpropanenitrile (1a) (1.0g, 11.7 mM) was dissolved in CH_2Cl_4 (10 mL) and treated with dihydropyran (1.50 mL, 13.2 mM) and p-TSA (10 mg). The resulting mixture was stirred for 2 h at ambient temperature. Workup and filtration of the crude product through a SiO_2 column gave the corresponding tetrahydropyranyl derivative 1b (1.90 g, 11.3 mM, 97%), which was characterized by ^{1}H NMR, IR, 13 C and mass spectrometry.

4.3 *General procedure for the preparation of methacryldehyde (3a)*

3-(5,6-dihydro-4H-pyran-2-yloxy)-2-methylpropanenitrile (1b) (1.0g, 5.9 mM) was taken in dry toluene (20 mL) at -78 ^{o}C under nitrogen. DIBAL (neat, 4 mL) was added dropwise to the above solution and the mixture was stirred for 1 hr. MeOH (5 mL) was added carefully after 1 hr, and the mixture was allowed to warm up to ambient temperature and then stirring continued overnight. The solution was filtered through Ceilite, the solvent removed, and the residue was chromatographed on a SiO_2 column (15 g, hexane- ethyl acetate) to give *methacryldehyde* (3a) (0.28g, 4.6 mM, 78%).

4.4 *Spectral data of representative end products 3a and 3g*

4.4.1 *Methylpropenal (3a)*

B.pt: 67-69°C, IR (KBr): 2845 (CH), 1730 (C=O); ^{1}H NMR ($CDCl_3$): δ 1.70 (s, CH_3), 5.93 (d, 1 H), 6.19 (d, 1 H); 9.66 (s, 1H). ^{13}C NMR (500 MHz**,** $CDCl_3$): δ 15.1, 132.7, 147.3, 193.3. MS (ESI, m/z 93) (M+Na). Anal. calcd. for C_4H_6O: C, 68.55; H, 8.63. Found C, 68.39; H, 8.69.

4.4.2 *3α-Hydroxy-5-pregn-20ξ-ene-20-carboxaldehyde (3g)*

Mp: 170-172°C, α_D: (+) 17. IR (KBr): 3600 (OH), 1680(C=O), 1620 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.56 and 0.99 (s, angular CH_3), 2.80 (t, 1 H, *J = 10 Hz*, 17-H), 5.36 (m, 1 H, 3-H); 6.12 (s, 1H), 6.30 (s, 1H), 9.56 (s, 1H). ^{13}C NMR (500 MHz**,** $CDCl_3$): δ 15.5, 20.9, 22.3, 24.0, 28.9, 30.5, 30.7, 39.0, 41.3, 46.4, 54.2, 58.7, 71.7, 75.7, 76.2, 109.9, 125.5, 128.4, 137.9, 145.6, 198.3. MS (ESI, m/z 351) (M+Na). Anal. calcd. for $C_{22}H_{32}O_2$: C, 79.95; H, 10.37. Found C, 79.89; H, 10.33.

5. ACKNOWLEDGEMENT

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