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Selective Reduction of α,β-Unsaturated Steroidal Carbonyl Compounds by $NaBH_4$ in Presence of Guanidine Hydrochloride in Dioxane

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A selective hydrogenation of α,β-unsaturated steroidal carbonyl compounds with $NaBH_4$ in the presence of guanidine hydrochloride in dioxane in good to excellent yields are described.

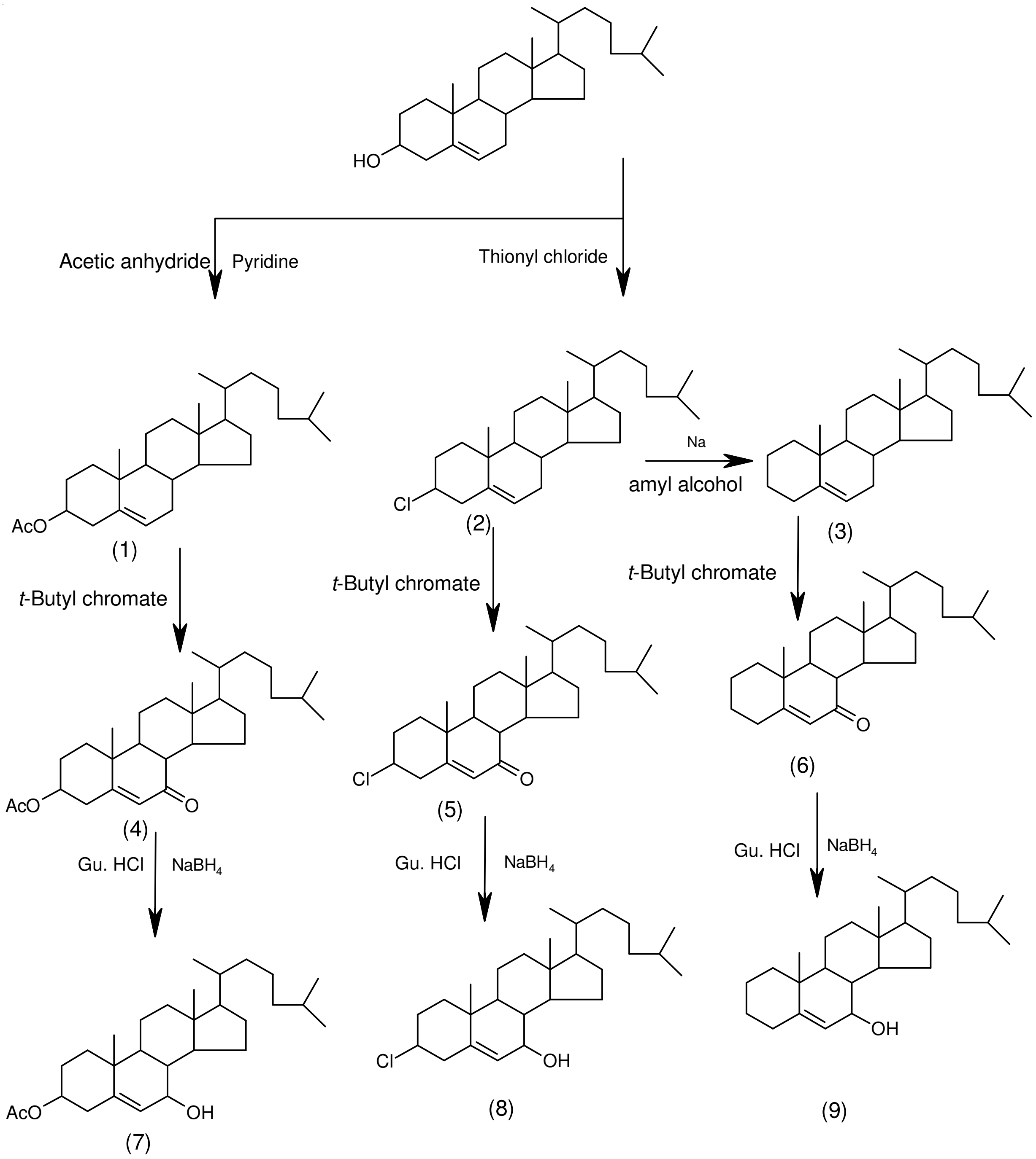
Keywords: Guanidine, Steroids, Dioxane, Reduction.

INTRODUCTION

Hydrogen-transfer reactions are advantageous with respect to other reduction methods because of several reasons[1] the hydrogen donor is easy to handle (no gas containment or pressure vessels are necessary), low-cost and environmentally friendly (*e.g.*, isopropanol)[2] possible hazards are minimized[3], the mild reaction conditions applied can afford enhanced selectivity[4], catalytic asymmetric transfer hydrogenation can be applied in the presence of chiral ligands[5,6]. The transfer hydrogenation of ketones has been mostly accomplished using isopropanol as hydrogen donor under homogeneous conditions in the presence of noble metal complexes (*e.g.*, Ru, Rh, Ni and Ir)[7,8]. In this field, ruthenium complexes have been by far the most studied catalysts, especially for the asymmetric transfer hydrogenation of aromatic ketones[9-11] and from the mechanistic point of view. It is worthwhile, however, developing new heterogeneous catalysts[12-14] that, generally, can simplify the catalytic system, use low-cost transition metals, simplify the purification step and be recycled and reused without significant loss of activity. In this sense, nickel appears as a potential alternative to the above expensive transition metal complexes but very less studied in hydrogen transfer reactions with isopropanol. It has been used either under homogeneous ($NiBr_2$- NaOH[15] and a macrocyclic nickel complex-NaOH[16]) or heterogeneous conditions ($NiCl_2$-i-PrOLi[17], Ni-stabilized zirconia-KOH[18] and mesoporous NiMCM-KOH[19]) mainly for aromatic substrates. In all these cases, the addition of an external base was mandatory for the reaction to take place. When a mixture of carbonyl compound is treated with appropriate reducing agent in a single operation it is termed a direct reductive alcohal reaction. A variety of reducing agents, such as hydrogen in the presence of metal catalysts[20], Bu_3SnH-DMF[21], $NaBH_3CN$[22], $NaBH(OAc)_3$[23], pyridine-BH_3[24] $NaBH_4$-$H_3P_{12}O_{40}$[25] have been developed. However, in terms of functional group tolerance, side reactions and reaction conditions such reducing agents have many limitations. For example, catalytic hydrogenation is attractive from economical and ecological viewpoints, despite its incompatibility with compounds containing other reducible functional groups such as carbon-carbon double or triple bond, cyano and furyl groups[26].

The direct reaction (a one-pot three component condensation reaction) is interesting and important, not only because two bonds are formed in one-pot, but in many cases, also offers considerable synthetic advantages in terms of broad variety of compounds and simplicity of the reaction procedure. Usually $NaBH_3CN$ and $NaBH(OAc)_3$ from commercial sources are utilized to carry out this transformation. It can be carried out under mild conditions and is compatible, in some cases, with many functional groups. However, the processes based on such reducing agents have many limitations. $NaBH_3CN$ is expensive and highly toxic and it may contaminate the product with NaCN and generate toxic HCN upon work-up[27]. Consequently, the selection of the reagents and conditions is very crucial. But no work on α,β-unsaturated steroidal carbonyl compounds. If one can perform the direct reduction of carbonyl compounds in air, it would be of considerable interest. Consequently, introduction of new procedure that alleviates or eliminates the above mentioned problems it should be a useful contribution in organic synthesis. We have approached this challenge to discover a new reagent from the viewpoint of both process and green chemistry. After surveying many of commercially available hydride reagents, we selected sodium borohydride as the least expensive, safe to handle and environmentally friendly reducing agent, which can particularly be used for large-scale reductions.

We report the results of our investigations for direct reduction of α,β-unsaturated steroidal carbonyl compounds by sodium borohydride/guanidine hydrochloride in dioxane. In addition, reactions in aqueous medium eliminate the additional efforts of preparing anhydrous substrates and reagents before use (**Scheme-I**). Unique properties of dioxan can be utilized to realize reactivity and selectivity that attained in organic solvents. At first, we carried out the reduction of α,β-unsaturated steroidal carbonyl compounds with using guanidine hydrochloride (5 mol %)/$NaBH_4$ in dioxane at room temperature and after the usual work up alcohol was obtained in 80-95 % isolated yield. These encouraging results prompted us to further investigate the use of guanidine hydrochloride/$NaBH_4$ as reducing agent. We have been studying the use of α,β-unsaturated steroidal carbonyl compounds for the synthesis of the corresponding allyl alcohols. Allyl alcohols are important intermediates in the production of pharmaceuticals, agrochemicals and fragrances. Chemo selective reduction of conjugated carbonyl compounds is a common reaction extensively used in synthetic chemistry and industry. Many useful methodologies for selective 1,2-reduction of α,β-unsaturated carbonyl compounds have been developed through metal



Scheme-I

hydride mediated reductions[28]. The most widely accepted of these involves sodium borohydride in the presence of cerium chloride. This has been optimized to give excellent selectivity under mild condition[29-32]. We now report that guanidine hydrochloride (5 mol %)/$NaBH_4$ in dioxane effects a facile and smooth reduction of α,β-unsaturated steroidal carbonyl compounds to produced exclusively the corresponding allylic alcohols.

EXPERIMENTAL

All the chemicals were purchased from Aldrich Chemical Company (U.S.A) and were used without further purification. The reactions were monitored by precoated aluminium silica gel 60F 254 thin layer plates procured from Merck (Germany). All melting points were measured with a capillary apparatus and are uncorrected. All the compounds were routinely checked by IR, ^{1}H NMR and mass spectrometry. IR spectra were recorded in KBr on a Perkin-Elmer model 1620 FTIR spectrophotometer. ^{1}H NMR spectra were recorded at ambient temperature using a Brucker spectroscopin DPX-400 MHz spectrophotometer in DMSO. FAB mass spectra were recorded on a JEOL SX102 mass spectrometer using argon/xenon (6 kV, 10 mB gas). Column chromatography was performed on silica gel (100-200 mesh). Anhydrous sodium sulfate was used as a drying agent for the organic phase.

General procedure: To a solution containing guanidine hydrocholiride (10 mg, 5 mol %) in dioxane (10 mL), was added the α,β-unsaturated steroidal carbonyl (2 mmol) (**4-6**) and the mixture vigorously stirred for 0.5 h at room temperature. After, $NaBH_4$ (2 mmol, 1 equiv.) was added, the mixture was stirred for additional 0.5 h. Progress of the reaction was monitored by TLC. The reaction mixture poured into ice cold water and extracted with CH_2Cl_2, dried over Na_2SO_4, concentrated under vacuum and the crude mixture was purified by column chromatography on silica gel (hexane:ethyl acetate, 2:1) to afford pure products (**7-9**).

3β-Acetoxycholest-5-en-7-ol ($C_{29}H_{48}O_3$) (7): semi-solid yields: 88 %; IR (KBr, ν_{max}, cm^{-1}): 3352 (OH), 2922 (C-H), 1626 (C=C). ^{1}HNMR (400 MHz, $CDCl_3$) δ: 5.45 (m, C6-H), 2.04 (s, 3H, CH_3OCO), 4.86 (br, m, w = 17 Hz, C3α-axical), 3.2 (m, C7-H), 2.4 (br, s, OH) 1.4 (C10-CH_3), 0.75 (C13-CH_3), 0.96, 0.84 (remaining methyl proton). Fab Mass (M^+.) at *m/z* 445. Anal. Calcd. For $C_{29}H_{48}O_3$: C, 78.37; H, 10.80; Found: C, 76.56; H, 9.52.

3β-Chlorocholest- 5-en-7-ol ($C_{27}H_{45}ClO$) (8): m.p. 106-108 °C, yields: 84 %; IR (KBr, ν_{max}, cm^{-1}): 3348 (OH), 2926 (C-H), 1622 (C=C), 728 (C-Cl). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.62 (m, C6-H), 4.52 (br, m, w = 15 Hz, C3α-axical), 3.5 (m, C7-H), 2.8 (br, s, OH) 1.6 (C10-CH_3), 0.72 (C13-CH_3), 0.94, 0.80 (remaining methyl proton). Fab Mass (M^+.) at *m/z* 423, Anal. Calcd. For $C_{27}H_{45}ClO$: C, 77.14 H, 10.71; Found: C, 76.45; H, 386;

Cholest-5-en-7-ol ($C_{27}H_{46}O$) (9): semi-solid, yields: 95 %; IR (KBr, ν_{max}, cm^{-1}): 3344 (OH), 2918 (C-H), 1628 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.28 (m, C6-H), 3.12 (m, C7-H), 2.24 (br, s, OH) 1.5 (C10-CH_3), 0.74 (C13-CH_3), 0.96, 0.85 (remaining methyl proton). Fab Mass (M^+.) at *m/z* 387. Anal. Calcd. For $C_{27}H_{46}O$: C, 83.93, H, 11.91; Found: C, 82.92; H, 10.5.

RESULTS AND DISCUSSION

The starting material 3β-acetoxycholest-6-one (**1**), 3β-chloro-cholest-6-one (**2**), 5α-cholest-6-one (**3**)[33,34] were prepared according to the published methods[16]. Reduction of α,β-unsaturated steroidal carbonyl compounds by sodium borohydride/guanidine hydrochloride in dioxan. as shown in **Scheme-I**[17]. All the compounds were soluble in DMSO and ethanol. The structures of all the compounds were established on the basis of spectral studies such as IR, ^{1}H NMR, FAB mass spectra and the elemental analyses were carried out to check the purity of the compounds.

Assignments of selected characteristic IR band positions provide significant indication for the reduction of α,β-unsaturated steroidal carbonyl compounds. All the compounds showed ν(C-OH) stretch at 3352-3344 cm^{-1} and absence of absorption band at 1700-1630 cm^{-1} also confirms the conversion of -C=O group to -C-OH group. Further evidence for the reduction of α,β-unsaturated Steroidal carbonyl compounds was obtained from the ^{1}H NMR spectra, which provide diagnostic tools for the positional elucidation of the protons. Assignments of the signals are based on the chemical shifts and intensity patterns. The reduction of α,β-unsaturated steroidal carbonyl compounds all the compounds is shown as brood singlet in the range 2.24-280 ppm, which is confirms the conversion of -C=O group to -C-OH group. Characteristic peaks were observed in the mass spectra of compounds **7-9**, which followed the similar fragmentation pattern. The spectrum of compound **7** showed a molecular ion peak ($M^{\bullet+}$) at *m/z* 445, compound **8** showed a molecular ion peak ($M^{\bullet+}$) at *m/z* 423 and compound **9** showed a molecular ion peak ($M^{\bullet+}$) at *m/z* 387. Further fragmentation pattern of these compounds has given in experimental section.

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