Chemoselective reduction of unsaturated γ- and δ-lactones by sodium borohydride in the presence of triethylamine in THF

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Abstract

α,β-Unsaturated γ- and δ-lactones were selectivity reduced to the corresponding saturated lactones and oxospiro systems respectively using sodium borohydride in the presence of triethylamine in THF, in excellent yields.

Keywords: Conjugate reduction, α,β-unsaturated lactones, sodium borohydride, spiro lactones

Introduction

It is well known, that many saturated lactones are displaying interesting biological activities and can be used in many various areas, especially, in medicine, pharmacology, perfume making, pesticides etc. Artemisinin and Santonin, endowed with valuable biological activity, are compounds containing saturated γ- and δ-lactone rings.[1,2] Many compounds, such as pilocarpine, a cholinergic drug, are also derivatives of γ-butanolides. Subsequent investigations, in the area of the synthesis of new derivatives of saturated γ-lactones are of great interest and can have a valuable potential for new biologically active compounds.[3]

Therefore, reduction of functionalized unsaturated lactones can be useful method for synthesizing functionalized saturated lactones, which would be otherwise difficult -if not impossible- to obtain.[4] There are known methods for synthesizing γ-butanolide, based on various organic oxides,[4] but unfortunately these reagents are not readily available.

Synthesis of functionalized unsaturated γ-lactones from 2,3-substitued α-hydroxy ketones and compounds with active methylene group is well documented and can easily be extended to the synthesis of unsaturated γ-lactones through double bond reduction with various reagents.[5] Catalytic hydrogenation is not always possible to apply because of unavailability of necessary catalysts and hydrogen hazards.[6] On the other hand, the reduction of butenolides by complex

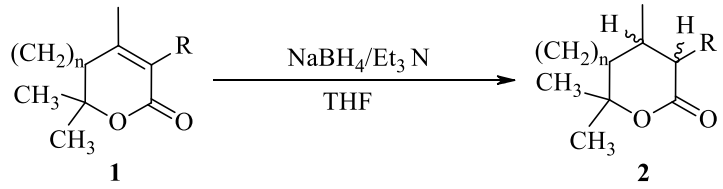
metal hydrides ($LiAlH_4$, $NaBH_4$) opens the lactone rings for production of the corresponding glycols.[7,8]

The report by Reddy *et al*.[9] who described the reduction of α-arylidene-γ-phenyl-β,γ-butenolides to the respective γ-butyrolactones in methyl alcohol with sodium borohydride in the presence of triethylamine, was for us very interesting.

Following the described method by Reddy using some unsaturated γ- and δ-lactones, in which C=C double bond of lactone ring is conjugated with present active functional groups (CN, CO_2Et, $COCH_3$, COOH, etc.), we tested $NaBH_4$ in the presence of triethylamine in THF, to reduce the C=C double bond of the ring in the mentioned lactones to obtain saturated derivatives of these compounds.

Results and Discussion

Metal hydrides are valuable reagents in modern organic chemistry. The most frequently used hydride is the $NaBH_4$ reagent. It is a mild, and inexpensive reagent used in a wide range of reduction processes. The reactivity and selectivity of $NaBH_4$ can be enhanced by carrying out the reaction in the presence of certain additives.[10] Reduction of unsaturated γ- and δ-lactones **1a-d** by $NaBH_4$ and Et_3N in THF at room temperature results in the production of the corresponding saturated lactones **2a-d** in high to excellent yields (Scheme 1).

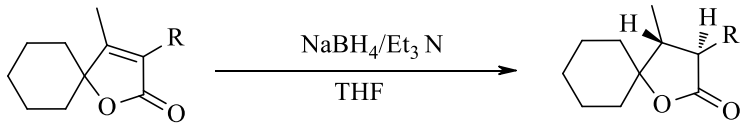


1 **2**

1, 2	n	R	Yields in **2**
a	0	H	86%
b	0	CN	91%
c	0	CO_2Et	83%
d	1	CN	95%

Scheme 1

Under similar conditions, the unsaturated oxospiro compounds **3a, 3b** also formed related saturated oxospiro systems in excellent yields (Scheme 2).



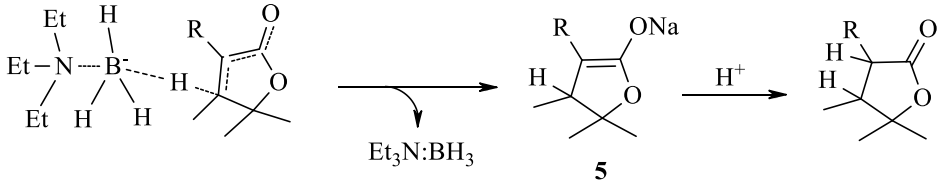
3 **4**

3, 4	R	Yields in **4**
	CN	98%
b	CO_2Et	96%

Scheme 2

The delocalization of the π-electrons of the ethylenic linkage, which occurs through conjugation of the carbon-carbon double bond with the ester, nitrile, phenyl, and/or amide groups present in various substrates, resulted in the creation of an electrophilic center which was capable of being attacked by a nucleophile, in this case the borohydride anion.

The exact mechanism for this reduction reaction is unclear. The presence of triethylamine is essential to modify the reactivity of $NaBH_4$ and achieve the required selectivity. A proposed mechanism for this reaction is outlined in Scheme 3 based on previous reports.[11]



Scheme 3

The structures of compounds **2a-2d** and **4a, 4b** were deduced from their IR, ^{1}H NMR and, ^{13}C NMR spectroscopy. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values, except for **2b**. In the mass spectrum of **2b**, the mass number is the largest ion with *m/z* 138, which likely corresponds to the fragment M^+-CH_3. Given the data ^{1}H and, ^{13}C NMR, this compound is a pure substance and corresponds to the structure attributed to it.

The IR spectrum of each isolated product exhibited the sharp absorption band of lactone carbonyl group at about 1740–1780 cm^{-1} and the absorption band for C = C double bond of lactone ring at 1660 cm^{-1} was not observed. The structures of all new compounds **2a-d** and **4a-b** were established by, ^{1}H NMR spectroscopy. In the, ^{1}H NMR spectrum of the products, a particular characteristic of the spectra is that the methyl protons at C4 are displaying a doublet at about δ = 1.07–1.20 ppm with $^3J_{HH}$ = 7.0 Hz. CH proton at C3 for the compound **2b** displayed a

doublet at δ = 4.37 ppm with $^{3}J_{HH}$ = 12.8 Hz and CH proton at C4 showed an AB_3X system (δ_A = 2.68, J_{AB} = 7.0 Hz, J_{AX} = 12.8 Hz). It was in agreement with the *anti* addition of hydrogens to the double bond of **1b**.[12] The methyl groups at C5 for **2b** are diastereotopic and exhibit two signals at 1.27 and 1.46 ppm. The, ^{13}C NMR spectrum of **2b** displayed eight distinct resonances in agreement with the 3-cyano-4,5,5-trimethyl-tetrahydrofuranone structure. Partial assignments of these resonances are given in the experimental section.

The ^{1}H and, ^{13}C NMR spectra of other products are similar to those of **2b**, except for the functional moieties, which exhibited characteristic resonances with appropriate chemical shifts. The *anti* addition of hydride to the double bond was also observed in, ^{1}H NMR spectra of other products (see Experimental Section).

Conclusions

In conclusion, we have demonstrated that sodium borohydride in the presence of triethylamine is an effective reagent for chemoselective reduction of unsaturated γ- and δ-lactones **1a-d** and also the unsaturated oxospiro compounds **3a-b**, which provides a number of interesting and novel 3-functionalized tetrahydrofuranones, that could be of value in a biological sense. These reactions are extremely clean with little by-product formation. Functional groups and lactone rings can all be reduced, but in these cases only conjugated carbon-carbon double bond with carbonyl was reduced efficiently.

Experimental Section

General. Melting points were measured with an Electrothermal 9100 apparatus. IR spectra were obtained on a Specord-751R IR spectrophotometer. NMR spectra were measured with a Varian Mercury-300 VX instrument (300.1 MHz for. ^{1}H and 75.5 MHz for. ^{13}C) with $CDCl_3$ as solvent. Chemical shifts are given in ppm (δ) relative to internal TMS, and coupling constant (*J*) are reported in Hertz (Hz). Mass spectra were recorded on a MX-1321A mass spectrometer operating at an ionization potential of 70 eV. Lactones were prepared by known methods.[5] Other reagents were obtained from Fluka (Buchs, Switzerland) and were used without further purification.

General synthetic procedure, exemplified by 4,5,5-trimethyltetrahydrofuran-2-one (2a)
To a magnetically stirred solution of 4,5,5-trimethyl-2(5*H*)-furanone **1a** (1.26 g, 0.01 mol) and triethylamine (2.02 g, 0.02 mol) in anhydrous THF (17 mL) was added $NaBH_4$ (0.4 g, 0.01 mol) portionwise at 0 ºC. The mixture was stirred at the same temperature for 15 min. The reaction mixture was then allowed to warm up to room temperature and stirred for 5 hrs. After acidification with 10% aqueous HCl solution to adjust its pH to 3-4, the reaction mixture was

extracted with ether (3×15 mL) and ether extract was washed with brine, dried $MgSO_4$ and evaporated to leave the crude product which was recrystallized from *n*-hexane, to give **2a**.

4,5,5-Trimethyl-tetrahydrofuranone (2a). White crystals, yield 86%, 1.1 g, mp 36–38 °C; IR (ν_{max}, cm^{-1}): 1740 (C = O). ^1H NMR (300.1 MHz, $CDCl_3$): δ_H 1.04 (3H, d, $^3J_{HH}$ = 6.5 Hz, CH_3), 1.23 (3H, s, CH_3), 1.40 (3H, s, CH_3), 2.23 (1H, ABX, J_{AB} = 15.8 Hz, J_{AX} = 10.2 Hz, CH_2), 2.31 (1H, m, CH), 2.60 (1H, ABX, J_{AB} = 15.8 Hz, J_{BX} = 6.7 Hz, CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 14.5 (CH_3), 21.9 (CH_3), 27.3 (CH_3), 36.9 (CH_2), 40.1 (CH), 86.7 (Me_2CO), 175.3 (C = O). MS, *m/z*(%) = 128 (M^+, 12), 113 (51), 84 (15), 70 (18), 69 (58), 59 (92), 43 (100).

3-Cyano-4,5,5-trimethyl-tetrahydrofuranone (2b). White solid, yield 91%, 1.4 g, mp 67–69 °C; IR (ν_{max}, cm^{-1}): 1780 (C = O), 2250 (C ≡ N). ^1H NMR (300.1 MHz, $CDCl_3$): δ_H 1.19 (3H, d, $^3J_{HH}$ = 7.0 Hz, CH_3), 1.27 (3H, s, CH_3), 1.46 (3H, s, CH_3), 2.68 (1H, dq, $^3J_{HH1}$ = 12.8 Hz, $^3J_{HH2}$ = 7.0 Hz, CH), 4.37 (1H, d, $^3J_{HH}$ = 12.8 Hz, CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 12.8 (CH_3), 21.5 (CH_3), 26.8 (CH_3), 39.6 and 46.2 (2CH), 86.7 (Me_2C), 114.4 (CN), 166.0 (C = O); MS, *m/z*(%) = 138 (M-15, 40), 121 (9), 109 (19), 94 (27), 59 (28), 43 (100).

3-Ethoxycarbonyl-4,5,5-trimethyl-tetrahydrofuranone (2c). White crystals, yield 83%, 1.65 g, mp 32–34 °C; IR (ν_{max}, cm^{-1}): 1770 and 1740 (C = O). ^1H NMR (300.1 MHz, $CDCl_3$): δ_H 1.10 (3H, d, $^3J_{HH}$ = 6.9 Hz, CH_3), 1.26 (3H, s, CH_3), 1.33 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3), 1.49 (3H, s, CH_3), 2.74 (1H, dq, $^3J_{HH1}$ = 12.4 Hz, $^3J_{HH2}$ = 6.9 Hz, CH), 3.27 (1H, d, $^3J_{HH}$ = 12.4 Hz, CH), 4.27 (2H, m, CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 13.1, 14.3, 22.1, and 26.8 ($4CH_3$), 44.4 and 53.9 (2CH), 62.0 (CH_2), 85.6 (Me_2C), 167.6 and 170.0 (2 C = O). MS, *m/z*(%) = 200 (M^+, 3), 185 (28), 156 (62), 141 (46), 114 (46), 111 (59), 86 (57), 83 (82), 43 (68).

3-Cyano-4,6,6-trimethyl-tetrahydropyranone (2d). White solid, yield 95%, 1.7 g, mp 80–82 °C; IR (ν_{max}, cm^{-1}): 1740 (C = O), 2260 (C ≡ N). ^1H NMR (300.1 MHz, $CDCl_3$): δ_H 1.20 (3H, d, $^3J_{HH}$ = 6.5 Hz, CH_3), 1.41 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.64 (1H, ABX, J_{AB} = 14.1 Hz, J_{AX} = 12.5 Hz, CH_2), 1.87 (1H, ABX, J_{AB} = 14.1 Hz, J_{BX} = 3.4 Hz, CH_2), 2.41 (1H, m, CH), 3.84 (1H, d, $^3J_{HH}$ = 11.9 Hz, CHCN). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 19.0 (CH_3), 27.2 (CH_3), 28.2 (CH), 29.6 (CH_3), 40.4 (CH), 40.4 (CH_2), 82.5 (Me_2C), 115.7 (CN), 162.8 (C=O). MS, *m/z*(%) = 167 (M^+, 2), 152 (10), 68 (58), 56 (100), 43 (90).

3-Cyano-4-methyl-5,5-pentamethylenetetrahydrofuranone (4a). White crystals, yield 98%, 1.9 g, mp 133–135 °C; IR (ν_{max}, cm^{-1}): 1780 (C = O), 2260 (C ≡ N). ^1H NMR (300.1 MHz, $CDCl_3$): δ_H 1.16 (3H, d, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.19–1.83 (10H, m, $5CH_2$), 2.64 (1H, m, CH), 4.32 (1H, d, $^3J_{HH}$ = 12.8 Hz, CHCN). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 11.8 (CH_3), 20.6, 21.9, 24.5, 29.1, and 34.5 ($5CH_2$), 38.1 and 44.9 (2CH), 87.3 (C-spiro), 115.1 (CN), 166.5 (C = O). MS, *m/z*(%) = 193 (M^+, 13), 150 (91), 83 (100), 69 (62), 68 (79), 55 (62), 41 (66).

3-Ethoxycarbonyl-4-methyl-5,5-pentamethylenetetrahydrofuranone (4b). White crystals, yield 96%, 2.3 g, mp 76–79 ºC; IR (ν_{max}, cm^{-1}): 1725 and 1760 (2 C = O). ^1H NMR (300.1 MHz, $CDCl_3$): δ_H 1.07 (3H, d, $^3J_{HH}$ = 6.9 Hz, CH_3), 1.31 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3), 1.23–1.77 (10H, m, $5CH_2$), 2.50 (1H, dq, $^3J_{HH1}$ = 12.3 Hz, $^3J_{HH2}$ = 6.9 Hz, CH), 3.51 (1H, d, $^3J_{HH}$ = 12.3 Hz, CH), 4.20 (2H, q, $^3J_{HH}$ = 7.1 Hz, CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C 12.3 and 13.6 ($2CH_3$), 20.7,

22.0, 24.6, 30.0, and 34.9 ($5CH_2$), 44.0 and 52.5 (2CH), 60.6 (OCH_2CH_3), 85.7 (C-spiro), 167.0 and 169.1 (2C = O). MS, *m/z*(%) = 240 (M^+, 4), 167 (25), 69 (77), 55 (51), 41 (100).

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