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Hydrazine hydrate induced reductive cleavage of α,β-epoxy ketones: an efficient procedure for the preparation of β-hydroxy ketones

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Abstract—An efficient and general procedure for the reductive cleavage of α,β-epoxy ketones to the corresponding β-hydroxy ketones, using hydrazine hydrate in ethanol at low temperatures, is described.

The selective reduction of α,β-epoxy ketones to β-hydroxy ketones is recognized as a synthetically important process in the construction of a variety of important natural products, through the use of these aldol key intermediates.

The aldol process proved to be highly useful for the preparation of 'acyclic' β-hydroxy ketones, however for cyclic β-hydroxy ketones this method cannot be generally applied efficiently.

Several methods have been developed to perform the selective reduction of α,β-epoxy ketones. Use of chromium(II) salts[1] and Zn/acetic acid[2] as well as electrochemical methods[3] often result in the formation of enone among other by products. Other examples include SmI_2,[4] Al amalgam,[5] Bu_3SnH/AIBN,[6] H_2/Pd/C,[7] PET,[8] organoselenium reagents,[9] photoinduced electron transfer reactions with 2-phenyl-*N*,*N*-dimethylbenzimidazoline[10] and lithium naphalenide,[11] but there are many drawbacks and disadvantages such as the need for the use of drastic conditions, poor yields, low selectivity, and the stoichiometric amounts of toxic reagents often required. Quite recently Doris and co-workers[12] reported the use of Cp_2TiCl for the selective reduction of α,β-epoxy ketones to β-hydroxy ketones.

In this communication we describe an efficient and versatile procedure for the reductive cleavage of α,β-epoxy ketones to the corresponding β-hydroxy ketones under mild conditions using $NH_2NH_2{\cdot}H_2O$ in ethanol as solvent. The steroidal epoxy ketones **1**, **7**, **10** and **13**, were readily reduced to corresponding β-hydroxy ketones **2**, **8**, **11**, **14** in high isolated yields (Scheme 1, Table 1). Apart from the reaction with substrate **10** at 0 °C, which required a mixture of ethanol/MTBE 2:3 as solvent, all the reactions were performed in ethanol. Temperature plays an important role in this procedure. Thus, reactions performed at low temperatures (−20 °C, 0 °C) afforded β-hydroxy ketones as the only product (Table 1 entries 1, 2, 8, 9, 13 and 17). Reactions performed under similar conditions but at room temperature afforded β-hydroxy ketones as major products (Table 1, entry 3, ratio β-hydroxy-ketone/allylic alcohol 2:1). In general, reactions carried out at 50 °C led to the mixtures of allylic alcohol and β-hydroxy-ketone (except for substrate **13**, Table 1, entry 19), while under reflux the allylic alcohol was the only reaction product (Table 1, entries 6, 7, 12, 16 and 18).

The reduction of α,β-epoxy ketones to allylic alcohols under these reaction conditions, corroborate with previous findings regarding the similar conditions used in the

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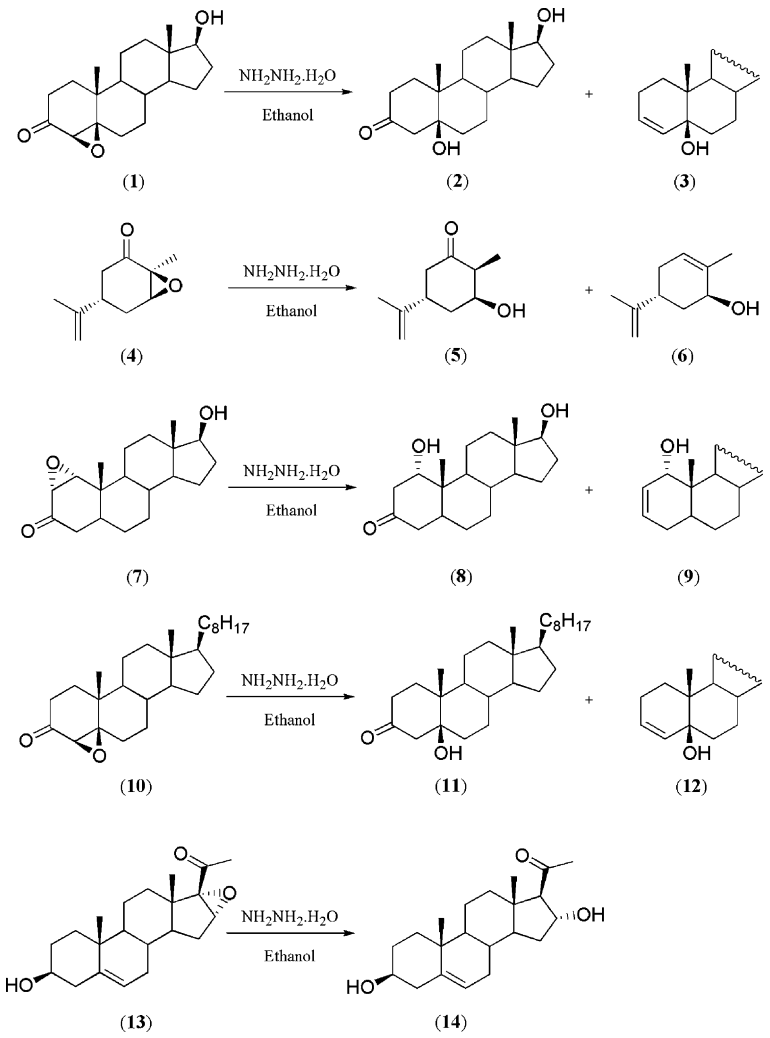

Scheme 1.

Wharton reaction (hydrazine hydrate, ethanol, acetic acid, reflux).[13]

The presence of water having no influence upon the reaction (Table 1 entries 5, 7, 13,15, 16 and 19) allows the use of a common solvent (ethanol) in this process.

The same outcome was generally observed with a non-steroid substrate **4**, the (*S*)-(+)-carvone epoxide. When the reaction was performed with this substrate at 0 °C, it afforded product **5** in a good yield (72%) and moderate stereoselectivity (Table 1, entry 9).

For the pregnane derivative **13**, the 20 keto group in a flexible side chain at C_{17} allowed to carry out the reaction at 50 °C leading to the formation of the corresponding β-hydroxy-ketone **14** (Table 1, entry 19). However, when the reaction was performed at reflux it afforded a mixture of the β-hydroxy-ketone **14** and the allylic alcohols.

Although the mechanism of this reaction is still unclear, using substrate **13**, we could isolate the 16α-hydroxy-20-hydrazone as the intermediate of the process before submitting the reaction solution to the acidic work-up.

In summary, the homogeneous mild reaction conditions and good yields in product formation, coupled with an operational simplicity broadness and reproducibility, in the aforementioned procedure, is a method of choice for the synthesis of β-hydroxy ketones via reductive cleavage of the corresponding α,β-epoxy ketones.

Typical procedure: To a solution of 4β,5β-epoxy-17β-hydroxyandrostan-3-one **1** (0.150 g/0.5 mmol) in ethanol at 0 °C, hydrazine hydrate (1 mL/20 mmol) was added. After 2 h under magnetic stirring, the solution was quenched with HCl (10% aq solution) and after 10 min extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layer was washed with aqueous saturated $NaHCO_3$ (2 × 25 mL), water (25 mL), dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to afford 5β,17β-dihydroxyandrostan-3-one **2** (0.131 g, 87%) as a white solid product.

Selected spectroscopic data: Spectroscopic data for **2**,[9b] **5**,[9a] **8**,[14] **11**[9a] and **14**[15] are in agreement with those reported in the literature.

Compound **2**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.77 (3H, s, 18-Me), 1.01 (3H, s, 19-Me), 3.04 (1H, d, J = 15.1 Hz,

Table 1. Reductive cleavage of α,β-epoxy ketosteroids and (*S*)-(+)-carvone epoxide with hydrazine hydrate

Entry	Substrate/mmol	Ethanol (mL)	Water (mL)	Hydrazine hydrate (mL)	Temperature (°C)	Time (h)	Product	Isolated yield (%)	Ratio[a] (hydroxy-ketone/allylic alcohol)
1	**1**/0.5	5	—	1.0	−20	2	**2**	86	1:0
2	**1**/0.5	5	—	1.0	0	2	**2**	87	1:0
3	**1**/0.5	5	—	1.0	rt	2	**2**	87	2:1
4	**1**/0.5	5	—	1.0	50	2	**2+3**	84	1:1
5	**1**/0.5	5	1.0	1.0	50	2	**2+3**	86	1:1
6	**1**/0.5	5	—	1.0	Reflux	2	**3**	87	0:1
7	**1**/0.5	5	1.0	1.0	Reflux	2	**3**	85	0:1
8	**4**/1.2	5	—	1.0	−20	2	**5**	70[b]	1:0
9	**4**/1.2	5	—	1.0	0	2	**5**	72[b]	1:0
10	**4**/1.2	5	—	1.0	rt	2	**5**	73	2.5:1
11	**4**/1.2	5	—	1.0	50	2	**6**	74	1:3.0
12	**4**/1.2	5	—	1.0	Reflux	2	**6**	73	0:1
13	**7**/0.16	2.5	0.1	0.3	0	3	**8**	84	1:0
14	**7**/0.16	2.5	—	0.3	rt	3	**8**	86	42:1
15	**7**/0.16	2.5	0.1	0.3	50	3	**8**	86	2:1
16	**7**/0.16	2.5	0.1	0.3	Reflux	3	**9**	88	0:1
17	**10**/0.25	2[c]	—	0.5	0	3	**11**	72[d]	1:0
18	**10**/0.25	5	—	0.5	Reflux	1	**12**	88	0:1
19	**13**/0.45	7.5	0.25	1.0	50	2	**14**	87	1:0

[a] Determined by ^{1}H NMR in crude product.
[b] The diastereoisomer (2*R*) was obtained in 33% yield as a by-product.
[c] A mixture of MTBE (3 mL) and ethanol (2 mL) was used as solvent.
[d] After flash chromatography (petroleum benzine–ethyl acetate 9:1–1:1).

4α-H), 3.67 (1H, t, $J = 8.5$ Hz, 17α-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 78.6 (C_5), 81.7 (C_{17}), 211.3 (C_3); IR (ATR): 3365, 2932, 2864, 1703, 1446, 1376, 1132, 1027, 1007, 955, 911 cm^{-1}.

Compound **5**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (3H, d, $J = 7.0$ Hz), 1.76 (3H, s), 4.32 (1H, m), 4.77 (1H, s), 4.80 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 73.6 (C_3); 110.0 (C=*C*H$_2$); 147.2 (*C*=CH$_2$); 210.9 (C_1); IR (Film): 3462, 3083, 2971, 2936, 1711, 1664, 1450, 1375, 1208, 1154, 1061, 985, 893 cm^{-1}.

Compound **8**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.75 (3H, s, 18-Me), 1.00 (3H, s, 19-Me), 2.67 (1H, dd, $J_1 = 15.4$ Hz, $J_2 = 3.3$ Hz, 4α-H), 3.61 (1H, t, $J = 8.5$ Hz, 17α-H), 4.07 (1H, t, $J = 3.1$ Hz, 1β-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 73.7 (C_1), 81.3 (C_{17}), 212.5 (C_3); IR (ATR): 3502, 3422, 2937, 1698, 1408, 1379, 1209, 1137, 1058, 1026, 997 cm^{-1}.

Compound **11**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.68 (3H, s, 18-Me), 0.86 (6H, d, $J = 6.6$ Hz, 26-Me and 27-Me), 0.92 (3H, d, $J = 6.6$ Hz, 21-Me), 1.00 (3H, s, 19-Me), 3.06 (1H, d, $J = 15.1$ Hz, 4α-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 78.7 (C_5), 211.5 (C_3); IR (ATR): 3437, 2947, 2867, 1711, 1624, 1467, 1380, 1000, 957, 733 cm^{-1}.

Compound **14**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.64 (3H, s, 18-Me), 1.01 (3H, s, 19-Me), 2.19 (3H, s, 21-Me), 2.57 (1H, d, $J = 6.5$ Hz, 17α-H), 3.48 (1H, m, 3α-H), 4.77 (1H, t, $J = 6.6$ Hz, 16β-H), 5.34 (1H, d, $J = 4.0$ Hz, 6-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 71.3 (C_{16}), 71.7 (C_{17}), 73.7 (C_3), 121.3 (C_6), 141.1 (C_5), 210.2 (C_{20}); IR (ATR): 3302, 2935, 2848, 1699, 1437, 1353, 1194, 1166, 1041, 948, 868 cm^{-1}.

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