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Effective and mild method for converting 3β-hydroxysteroids to 3-keto steroids via DDQ/TEMPO

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ABSTRACT

A mild and efficient oxidation of 3β-hydroxysteroids to the corresponding 3-keto steroids can be carried out at room temperature, using DDQ in the presence of catalytic TEMPO. Oxidation of saturated 3β-hydroxysteroids gave the corresponding ketones in excellent yield. The 5-unsaturated 3β-hydroxysteroids are oxidized selectively to 4-en-3-one or 4,6-diene-3-one derivatives according to the amount of DDQ in reaction. This is a good method for the synthesis of 4,6-diene-3-one from the corresponding 3β-hydroxy-5-ene steroids. Meanwhile, configurations of the oxidation compounds **2a**, **2b**, **3b**, **2c**, **2f** and **2g** were identified by X-ray diffraction. A possible mechanism is presented and discussed.

1. Introduction

Steroidal ketones are important intermediates to synthesize a wide variety of vital biologically active steroid hormones, including control of carbohydrate metabolism (glucocorticoids), reproduction (male and female sexual hormones), as well as antibacterial and antitumor activities [1–3]. It is necessary to study of the synthesis of steroidal ketones due to the large-scale industrial production of steroid drugs. Previous studies have shown that the introduction of 3-one based on Cr(VI) reagents proved to be capricious in this particular case and hardly applicable to industry on a large scale [4]. Steroidal 4-ene-3-ones are synthesized by oxidation of 3β-hydroxy-5-en steroids with the classical Oppenauer oxidation using $(i\text{-PrO})_3Al$ and a large excess of cyclohexanone. With this method, however, the product is always contaminated with the substances of aldol condensation of cyclohexanone, for whose separation steam distillation has to be used, further increasing the cost. Steroidal 4,6-diene-3-ones are synthesized by oxidation of 3β-hydroxy-5-en steroids with MnO_2 or aluminum isopropoxide [5–6]. However, these methods give pretty low yield. Steroidal 4,6-diene-3-ones can also be are synthesized by dehydrogenation of steroidal ketones with 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ) or chloranil [7].

In recent years, 2,2,6,6-tetramethyl piperidinyl 1-oxyl (TEMPO) catalyzed alcohol oxidation has gained increasing priority not only in academic laboratories, but also in the chemical industries, particularly in the pharmaceutical industry, as an efficient, mild, and environmentally acceptable method [8–10]. DDQ are powerful oxidants capable of performing a wide variety of organic transformations [11,12]. Initially introduced for the dehydrogenation agent in the 1950's [13], its use was extended to the steroids field. Previous review articles on DDQ have been published, which may provide readers with a more in depth perspective [14–17]. The oxidation of alcohols to the corresponding carbonyl compounds by using DDQ and co-oxidant has been developed, for example, Shen et al. [18] have recently demonstrated the selective oxidation of non-sterically hindered benzylic alcohols using catalytic amounts of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and tert-butyl nitrite with molecular oxygen. Wang et al. [19] have developed for the oxidation of allylic and propargylic alcohols over benzylic alcohols to the corresponding carbonyl compounds by using DDQ, $NaNO_2$ as a cocatalyst, and molecular oxygen as terminal oxidant. Cosner et al. [20] have described chemoselective oxidation of electron-rich benzylic alcohols and allylic alcohols employing DDQ as the oxidant and $Mn(OAc)_3$ as the co-oxidant. DDQ was used for selectively oxidations steroidal allylic alcohol to the corresponding αβ-unsaturated ketone in excellent [21]. Steroidal 5-en-3-ol(s) can be oxidized directly to 1,4,6-trien-3-one by DDQ at reflux [22]. DDQ oxidation of alcohols appears to be even more strongly

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dependent upon steric factors than chromic acid oxidation [23]. Hence, there is clearly a need for a more efficient method of the oxidation of sterol with DDQ. Herein we report the oxidation of 3β-hydroxysteroids to 3-keto steroids with DDQ/TEMPO coupled at room temperature, where catalytic amounts of TEMPO are used in combination with DDQ as stoichiometric oxidation.

2. Experiment

Melting points were determined using a WRS-1B apparatus and were uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on 600/150 MHz NMR spectrometers (a Bruker AV600 spectrometer), using tetramethylsilane (TMS) as the internal standard and $CDCl_3$ as the solvent. High resolution mass (HRMS) spectra were obtained in ESI mode on a Finnigan MAT95XP HRMS system (Thermo Electron Corporation). Diffraction experiments for oxidation product were carried out on with Mo Ka radiation (λ = 0.71073 Å) using a bruker SMART APEX CCD diffractometer at 296 K. All chemicals were of reagent grade and used as commercially purchased without further purification. All solvents were dried and distilled before use. The reactions were monitored by TLC on silica gel 60 F_{254}. Chromatography was conducted by using 200–300 mesh silica gel.

2.1. General procedure

To a stirred solution of steroids (1 mmol) in dry CH_2Cl_2 at 0 °C was added DDQ (1.2 mmol or 2.2 mmol) and TEMPO (0.1 mmol). After the addition, the mixture was warmed to room temperature and stirred for the required time until completion by TLC. The mixture was filtered on Celite, the filtrate was respectively washed with 2% sodium hydroxide, saturated sodium chloride solution and distilled water. The solution was dried, concentrated in a rotovap. The residue was then purified by flash chromatography (petroleum ether/ethyl acetate) to obtain the desired product.

2.2. 5α-Spirostan-3-one (**2a**)

5α-Spirostan-3-one (**2a**) from tigogenin (**1a**). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 4.40 (q, *J* = 11.2 Hz, 1H), 3.39 (m, 1H), 3.37 (t, *J* = 10.8 Hz, 1H), 1.02 (s, 3H), 0.96 (d, *J* = 3.6 Hz, 3H), 0.79 (s, 3H), 0.78 (d, *J* = 2.0 Hz, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ: 212.0, 109.3, 80.8, 67.0, 62.3, 56.3, 54.0, 46.7, 44.8, 41.7, 40.7, 40.0, 38.6, 38.3, 35.8, 35.2, 32.0, 31.8, 31.4, 30.4, 29.0, 28.9, 21.3, 17.2, 16.5, 14.7, 11.7 ppm. HRMS: [M+] calcd for $C_{27}H_{42}O_3$: 414.3134; found: 414.3138.

2.3. Methyl 3-oxo-androst-4-ene-17β-carboxylate (**2b**)

Methyl 3-oxo-androst-4-ene-17β-carboxylate (**2b**) from 3β-hydroxy-5-androstene-17β-carboxylate (**1b**). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 5.73 (s, 1H), 3.66 (s, 3H), 1.18 (s, 3H), 0.69 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ: 199.6, 174.5, 124.1, 118.1, 56.2, 55.2, 54.9, 53.5, 44.0, 42.7, 38.1, 37.8, 35.7, 34.0, 32.3, 31.7, 24.4, 23.6, 20.9, 19.1, 13.5 ppm. HRMS: [M+] calcd for $C_{21}H_{30}O_3$: 330.2195; found: 330.2199.

2.4. Methyl 3-oxo-androst-4,6-diene-17β-carboxylate (**3b**)

Methyl 3-oxo-androst-4,6-diene-17β-carboxylate (**3b**) from 3β-hydroxy-5-androstene-17β-carboxylate (**1b**). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 6.10 (s, 2H), 5.70 (s, 1H), 3.67 (s, 3H), 1.10 (s, 3H), 0.74 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ: 197.6, 175.5, 155.9, 132.6, 126.1, 121.1, 55.7, 48.0, 46.5, 42.5, 39.0, 38.9, 38.1, 31.0, 28.5, 20.9, 20.3, 20.1, 19.1, 18.9, 13.7 ppm. HRMS: [M+] calcd for $C_{21}H_{28}O_3$: 328.2038; found: 328.2042.

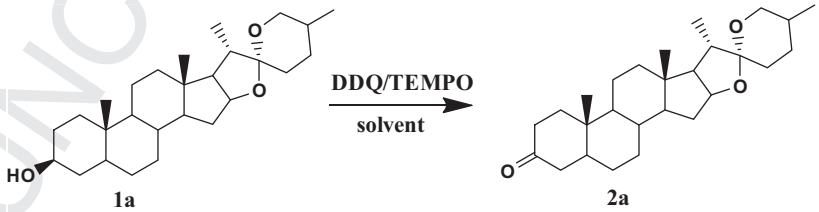
2.5. 25(R)-4,6-Spirostadien-3-one (**2c**)

25(R)-4,6-Spirostadien-3-one (**2c**) from (3β, 25R)-spirost-5-en-3-ol (**1c**). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 6.11 (d, *J* = 2.4 Hz, 2H), 5.67 (s, 1H), 1.26 (s, 3H), 0.98 (d, *J* = 6.4 Hz, 3H), 0.88 (s, 3H), 0.79 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ: 199.7, 163.8, 141.0, 128.1, 123.9, 109.5, 80.6, 67.1, 62.2, 53.3, 50.9, 41.8, 41.6, 39.7, 37.4, 36.3, 34.1, 34.0, 31.5, 31.4, 30.4, 28.9, 20.6, 17.3, 16.5, 16.4, 14.6 ppm. HRMS: [M+H+] calcd for $C_{27}H_{39}O_3$: 411.2821; found: 411.2825.

2.6. Pregna-4,6-diene-3,20-dione (**2d**)

Pregna-4,6-diene-3,20-dione (**2d**) from 3β-hydroxy-5-pregnene-20-one (**1d**). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 6.12 (d, *J* = 2.4 Hz, 2H), 5.69 (s, 1H), 2.15 (s, 3H), 1.12 (s, 3H), 0.72 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ: 208.8, 199.5, 163.3, 140.6, 128.3, 123.9, 63.4, 53.8, 50.7, 44.8, 38.7, 37.7, 36.2, 34.0, 34.0, 31.6, 24.0, 23.0, 20.8, 16.4, 13.4 ppm. HRMS: [M+] calcd for $C_{21}H_{28}O_2$: 312.2089; found: 312.2091.

Table 1
The oxidation of tigogenin with DDQ in the presence of TEMPO.



1a 2a

Entry	Solvent	Reaction time (h)	Yield (%)
1	CH_2Cl_2	24	80.2
2	Toluene	24	30.4
3	Dioxane	24	50.8
4	$CHCl_3$	24	73.6
5	Ethyl acetate	24	36.4
6	$ClCH_2CH_2Cl$	24	71.4

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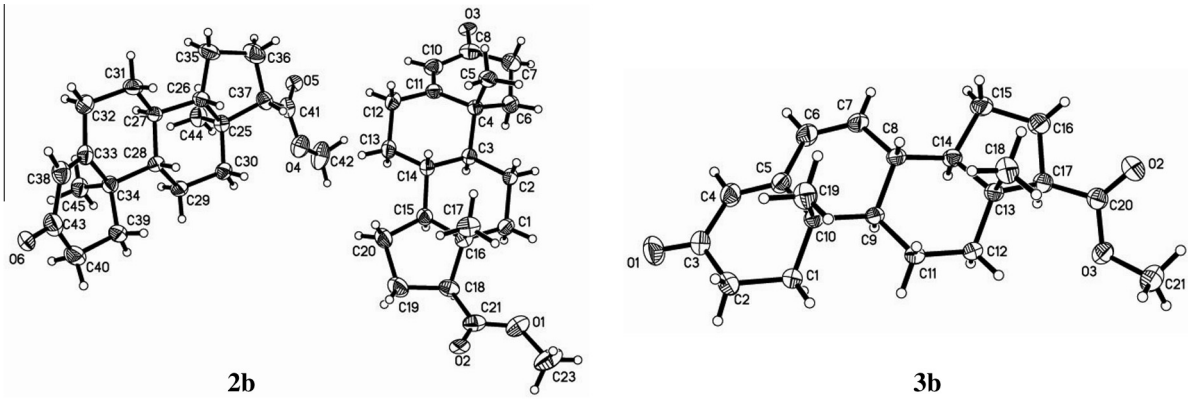
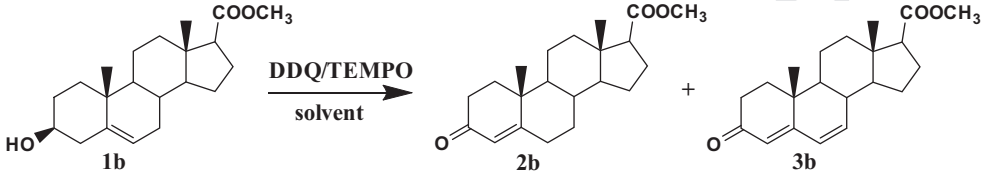


Fig. 1. X-ray diffraction crystal structures of **2b** and **3b**.



Scheme 1.

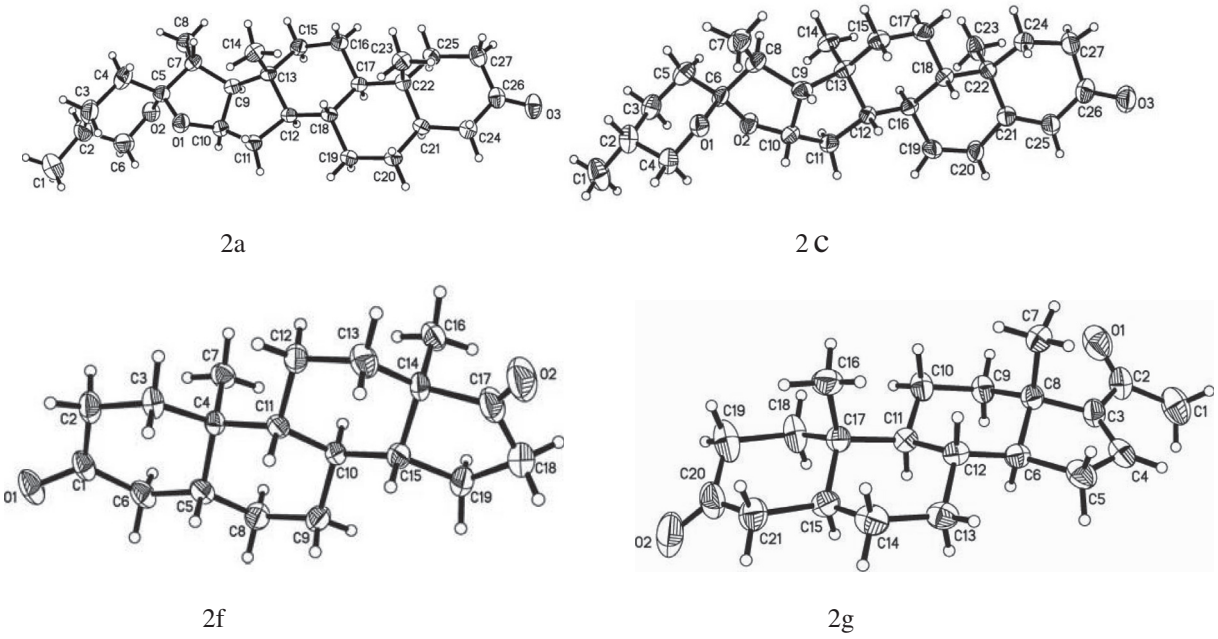


Fig. 2. X-ray diffraction crystal structures of **2a**, **2c**, **2f** and **3b**.

*2.7. Androsta-4,6-diene-3,17-dione (**2e**)*

Androsta-4,6-diene-3,17-dione (**2e**) from 17β-hydroxy-5-androst-17-one (**1e**). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 6.18 (s, 2H), 5.70 (s, 1H), 1.14 (s, 3H), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz), δ: 219.7, 199.6, 163.1, 138.6, 129.0, 124.4, 51.0, 49.0, 48.5, 37.2, 36.4, 35.9, 34.1, 34.1, 31.5, 21.7, 20.2, 16.6, 13.9 ppm. HRMS: [M+] calcd for $C_{19}H_{24}O_2$: 284.1776; found: 284.1779.

*2.8. Androstane-3,17-dione (**2f**)*

Androstane-3,17-dione (**2f**) from 3β-hydroxy-17-androstanone (**1f**). ^{1}H NMR (600 MHz, $CDCl_3$): δ: 1.04 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz), δ: 220.9, 211.5, 53.9, 51.2, 47.7, 46.6, 44.5, 38.4, 38.0, 35.8, 35.8, 34.9, 31.5, 30.5, 28.6, 21.7, 20.7, 13.8, 11.4 ppm. HRMS (M+) for $C_{19}H_{28}O_2$, calcd 288.2089, found 288.2084.

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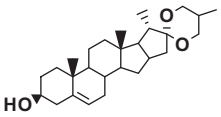
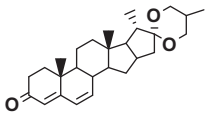
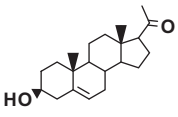
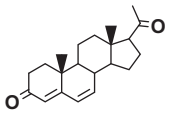
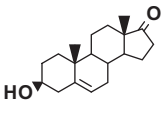
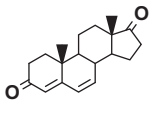
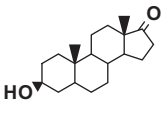
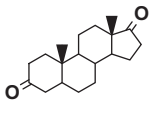
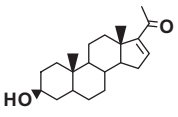
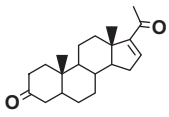
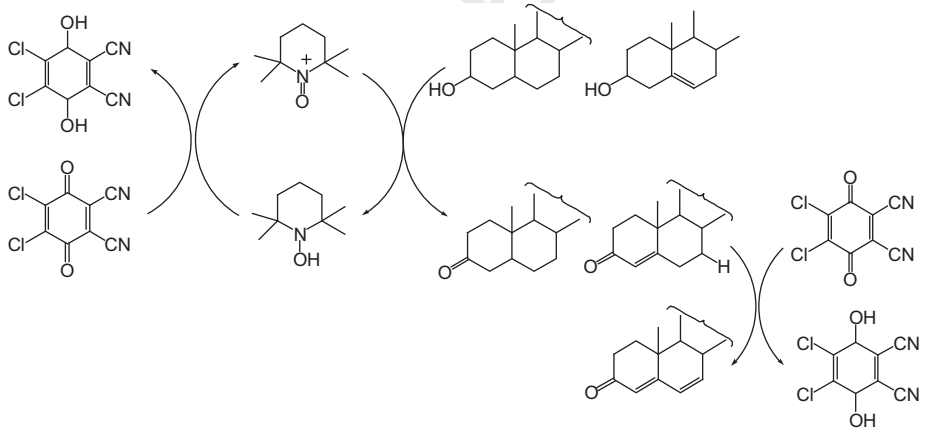
Table 2
Oxidations of 3β-hydroxy steroids with DDQ/TEMPO system.

Entry	Reactant	Product	Steroid/DDQ	Time (h)	Yield (%)
1	 **1c**	 **2c**	1/2.2	36	68.3
2	 **1d**	 **2d**	1/2.2	36	70.2
3	 **1e**	 **2e**	1/2.2	36	71.5
4	 **1f**	 **2f**	1/1.2	24	82
5	 **1g**	 **2g**	1/1.2	24	78



Scheme 2.

2.9. Pregn-16-ene-3,20-dione (**2g**)

Pregn-16-ene-3,20-dione (**2g**) from 3β-hydroxy-5α-pregn-16-en-20-one (**1g**).

^{1}H NMR (600 MHz, $CDCl_3$): δ: 6.69 (m, 1H), 2.26 (s, 3H), 1.04 (s, 3H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) : δ: 208.6, 196.7, 146.0, 136.5, 43.5, 42.3, 39.0, 37.6, 37.1, 36.8, 36.3, 32.2, 32.0, 30.9, 28.8, 25.7, 24.8, 23.0, 20.8, 16.8, 13.6 ppm. HRMS (M+H+) for $C_{21}H_{31}O_2$, calcd 315.2246, found 315.2250.

3. Results and discussion

Initially, in order to explore this reaction condition, we selected tigogenin (**1a**) as the substrate for the investigation of the effect of different solvents for the same reaction (Table 1). When tigogenin (**1a**) and DDQ (1.2 eq) were reacted in the presence of 10% TEMPO at room temperature, the data in Table 1 shows that the solvents do have a major effect on the yield. The highest yield was obtained by utilizing CH_2Cl_2 as solvent (see Fig. 1).

When methyl 3β-hydroxy-5-androstene-17β-carboxylate (**1b**) and DDQ (1.2 eq) were reacted in the presence of 10% TEMPO in CH_2Cl_2 at room temperature, unexpectedly, two compounds, methyl 3-oxo-androst-4-ene-17β-carboxlate (**2b**) and methyl 3-oxo-androst-4,6-diene-17β-carboxylate (**3b**) were produced at a 80:20 ratio with a total yield of 75% (Scheme 1). Further optimization showed that increasing the amount of DDQ (2.2 eq) could yield a 80% conversion as well as 98: 2 **3b**/**2b** ratio. The configurations of the compounds **2b** and **3b** were confirmed by X-ray crystal diffraction analysis (Fig. 2).

Under the above optimized conditions, the protocol was applied to another five 3β-hydroxysteroids, and corresponding products were isolated in gram quantities with moderate to good yields

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ranging from 68.3% to 82% (Table 2, entries 1–5). Incidentally, this is a good method for the synthesis of 4,6-diene-3-one derivatives from the corresponding 3β-hydroxy-5-ene steroids. It is important to mention that under our reaction conditions, no 1,4-diene-3-one was observed. The configurations of the compounds **2c**, **2f** and **2g** were confirmed by X-ray crystal diffraction analysis (Fig. 2).

A possible mechanism for the oxidation of steroidal alcohols is proposed in Scheme 2. The alcohol is oxidized by $TEMPO^+$ to obtain the desired oxidation product and TEMPOH. TEMPOH could be converted into $TEMPO^+$ by reaction with DDQ, which resulted in DDHQ. The mechanism by which DDQ affects 4,6-diene-3-one is believed to involve an initial rate-determining transfer of hydride ion from the steroids followed by a rapid proton transfer leading to hydroquinone formation [14,24].

4. Conclusion

In summary, a mild and efficient procedure was developed for the oxidation of 3β-hydroxysteroids in the DDQ/TEMPO system at room temperature. This methods allows to synthesize 4,6-diene-3-one derivatives from the corresponding 3β-hydroxy-5-ene steroids in a single step. Moreover, under these mild conditions, no 1,4-diene-3-one were detected. Thus, the procedure described offers significant advantages over previous oxidation methods.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.steroids.2015.01.010.

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