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A practical Δ^1-dehydrogenation of Δ^4-3-keto-steroids with DDQ in the presence of TBDMSCl at room temperature

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ABSTRACT

A mild and efficient Δ^1-dehydrogenation of Δ^4-3-keto-steroids with DDQ in the presence of tert-butyldimethylchlorosilane at room temperature was developed.

1. Introduction

Δ^1-Dehydrogenation of abundantly available Δ^4-3-keto-steroids for getting more effective therapeutic drugs is one of the important reactions in steroid chemistry [1]. Microbiological Δ^1-dehydrogenation method is frequently used for the preparation of $\Delta^{1,4}$-3-keto-steroids [2,3]. The main disadvantage of this method is that large volumes of solution are required, and enzymes may create handling and stabilization difficulties. Moreover, equipment price is much higher than for classical chemical reactions. The chemical Δ^1-dehydrogenation of Δ^4-3-keto-steroids by treatment with 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ) has been intensively investigated. The reaction is performed at relative high (>100 °C) temperatures always in the presence of acids such as HCl, p-TsOH, p-nitrophenol and salicylic acid [4–10]. Under this condition some amounts of $\Delta^{4,6}$-3-keto-steroid, $\Delta^{1,4,6}$-3-keto-steroid and degraded products were always formed [11]. The DDQ oxidation of trimethylsilylenol ethers giving enones with high yield by thermolysis of quinone–substrate adducts has been reported [12–15]. This process stimulated us to examine the Δ^1-dehydrogenation of Δ^4-3-keto-steroid with DDQ catalyzed by chlorosilane agent. In this paper we will report a practical Δ^1-dehydrogenation of Δ^4-3-keto-steroids with DDQ in the presence of TBDMSCl at room temperature.

2. Experimental

Melting points were determined with a RY-1 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker-500 NMR spectrometer, and chemical shifts δ are in ppm (TMS are used as an internal standard). EI mass spectra were accomplished at 70 eV, using a MAT 90 spectrometer. Microanalyses were performed on a Leco CHN-2000 elemental analyzer. Optical rotations were taken on a Perkin-Elmer 341 polarimeter at the sodium-D line. All chemicals were purchased from commercial sources and were used without further purification unless otherwise noted.

2.1. General procedure

To a solution of Δ^4-3-keto-steroid (10 mmol) and TBDMSCl (0.5 mmol) in 10 ml dioxane was added DDQ (13 mmol) in two portions at 0 °C. The reaction mixture was warmed to room temperature with vigorous stirring. The progress of the reaction was checked by TLC. The suspension was diluted with chloroform (50 ml). The organic layer was consecutively washed with water (2 × 20 ml), 5% NaOH (3 × 20 ml) [16] and water (2 × 20 ml) then dried with Na_2SO_4 and evaporated in vacuum. The pale yellow residue was crystallized with hexane/ethyl acetate to afford the desired product.

2.2. Androst-1,4-diene-3,17-dione (**2a**)

Mp. 141.5–142 °C; $[\alpha]_D^{20}$ 118° (c 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.92 (s, 3H), 1.10–1.20 (m, 2H), 1.23–1.34 (m, 2H), 1.27 (s, 3H),

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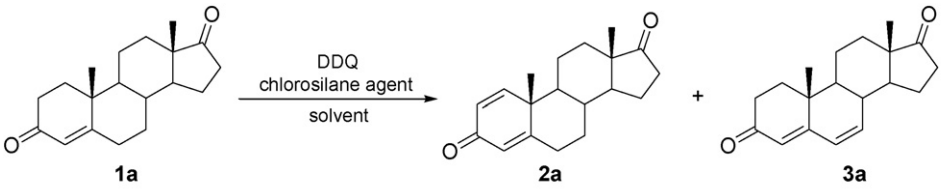
Table 1
Δ^1-Dehydrogenation of AD with DDQ in the presence of chlorosilane agents.[a]



Entry	Solvent	Silylating agent	Reaction time (h)	Conversion	**2a**/**3a**[b]
1	Benzene	$(CH_3)_3SiCl$	24	81.5	75/25
2	Benzene	–	24	NR	–
3	$CHCl_3$	$(CH_3)_3SiCl$	24	78.4	70/30
4	Dioxane	$(CH_3)_3SiCl$	24	93.5	75/25
5	Dioxane	HCl	24	NR	–
6	Dioxane	$(CH_3)_3SiCl + Et_3N$	24	NR	–
7	Dioxane	$^tBu(CH_3)_2SiCl$	30	90.4	94/6
8	Dioxane	Et_3SiCl	24	83.3	85/15
9	Dioxane	$^tBuPh_2SiCl$	36	90.3	94/6
10	Dioxane	BSTFA	24	NR	–
11	Dioxane	$^tBu(CH_3)_2SiCl$[c]	48	92.7	95/5
12	Dioxane	$^tBu(CH_3)_2SiCl$[d]	48	77.8	95/5

[a] Unless otherwise indicated, reactions have been carried out at room temperature in the presence of silylating agents (0.05 equiv.) for 24 h.
[b] The ratio of **2a**/**3a** was determined by NMR.
[c] DDQ was added at 0 °C.
[d] TBDMSCl 0.025 equiv.

1.55–1.78 (m, 2H), 1.79–1.92 (m, 3H), 1.93–2.02 (m, 1H), 2.03–2.18 (m, 2H), 2.38–2.58 (m, 3H), 6.10 (d, J = 1.0 Hz, 1H), 6.25 (dd, J = 1.5, 10.0 Hz, 1H), 7.05 (d, J = 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 13.8, 18.7, 21.9, 22.1, 31.2, 32.3, 32.5, 35.1, 35.6, 43.4, 47.7, 50.4, 52.3, 124.1, 127.7, 155.3, 168.2, 186.2, 219.9; MS (EI): m/z 284 (M^+, 12%), 122 (100%); Anal. calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.14; H, 8.87.

2.3. 17β-Hydroxy-17α-methyl-androsta-1,4-diene-3-one (**2b**)

Mp. 148.3–150.5 °C; $[\alpha]_D^{20}$ −1.8° (c 1.12, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.94 (s, 3H), 0.99–1.07 (m, 2H), 1.17–1.22 (m, 1H), 1.19 (s, 3H), 1.25 (s, 3H), 1.24–1.40 (m, 3H), 1.55–1.90 (m, 7H), 1.94–2.00 (m, 1H), 2.34–2.38 (m, 1H), 2.44–2.52 (m, 1H), 6.07 (t, J = 1.5 Hz, 1H), 6.23 (dd, J = 1.5, 10.0 Hz, 1H), 7.07 (d, J = 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 14.0, 18.7, 22.6, 23.4, 25.8, 31.3, 32.8, 33.3, 36.3, 38.7, 43.6, 45.6, 49.8, 52.4, 81.3, 123.8, 127.4, 156.0, 169.3, 186.4; MS (EI): m/z 300 (M^+, 8%), 122 (100%); Anal. calcd. for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39; Found: C, 80.12; H, 9.23.

2.4. 17β-Hydroxyandrosta-1,4-diene-3-one (**2c**)

Mp. 166–167 °C; $[\alpha]_D^{20}$ 27° (c 1.07, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.83 (s, 3H), 0.93–1.12 (m, 4H), 1.24 (s, 3H), 1.29–1.38 (m, 1H), 1.39–1.50 (m, 2H), 1.60–1.72 (m, 2H), 1.74–1.80 (m, 1H), 1.85–1.97 (m, 2H), 2.03–2.10 (m, 1H), 2.34–2.10 (m, 1H), 2.43–2.50 (dt, J = 4.5, 12.0 Hz, 1H), 3.64 (m, 1H), 6.07 (t, J = 1.5 Hz, 1H), 6.30 (dd, J = 2.0, 10.0 Hz, 1H), 7.06 (d, J = 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 11.2, 18.7, 22.5, 23.5, 30.4, 32.8, 33.1, 35.6, 36.3, 43.1, 43.6, 50.1, 52.5, 81.5, 123.9, 127.5, 155.8, 169.1, 186.4; MS (EI): m/z 286 (M^+, 2%), 122 (100%); Anal. calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15; Found: C, 79.55; H, 9.12.

2.5. Estra-1,3,5(10)-triene-3,17-diol (**2d**)

Mp. 166–168 °C; $[\alpha]_D^{20}$ 77° (c 0.89, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.83 (s, 3H), 1.09–1.18 (m, 3H), 1.30–1.55 (m, 4H), 1.76–1.90 (m, 3H), 2.07–2.16 (m, 2H), 2.24–2.47 (m, 3H), 2.52 (d, J = 2.0 Hz, 1H), 3.71 (t, J = 8.0 Hz, 1H), 5.78 (s, 1H), 6.18 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 10.9, 22.8, 25.1, 27.0, 30.3, 36.3, 37.8, 40.9, 41.4, 43.8, 46.1, 48.0, 81.4, 124.4, 128.7, 141.7, 158.9, 200.1; MS (EI): m/z 272 (M^+, 60%), 133 (100%); Anal. calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.48; H, 8.80.

2.6. Phenol (**2e**)

Mp. 39.5 °C; ^{1}H NMR ($CDCl_3$): δ 4.77 (s, 1H), 6.83 (dd, J = 1.0, 8.0 Hz, 1H), 6.94 (t, J = 8.0 Hz, 1H), 7.54 (dd, J = 2.5, 8.0 Hz, 1H).

2.7. 6-Methylenandrost-1,4-diene-3,17-dione (**2f**)

Mp. 196–197 °C; $[\alpha]_D^{20}$ 278° (c 1.19, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.95 (s, 3H), 1.17 (s, 3H), 1.23–1.27 (m, 2H), 1.31–1.40 (m, 3H), 1.58–1.77 (m, 2H), 1.88–1.97 (m, 3H), 1.98–2.03 (m, 1H), 2.08–2.17 (m, 1H), 2.46–2.53 (m, 1H), 2.58–2.67 (m, 1H), 5.00 (d, J = 2.0 Hz, 1H), 5.07 (t, J = 2.0 Hz, 1H), 6.25 (dd, J = 2.0, 10.0 Hz, 1H), 7.07 (d, J = 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 13.8, 19.7, 21.8, 22.0, 31.2, 35.3, 35.6, 39.3, 43.7, 47.6, 50.0, 50.8, 112.5, 122.8, 127.9, 145.3, 154.0, 167.2, 186.3, 219.6; MS (EI): m/z 296 (M^+, 11%), 148 (100%); Anal. calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16; Found: C, 81.21; H, 8.11.

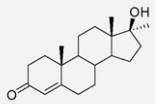
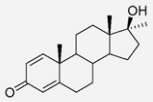
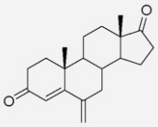
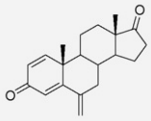
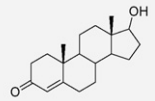
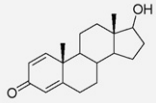
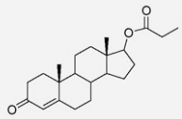
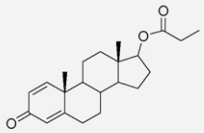
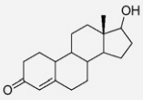
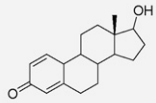
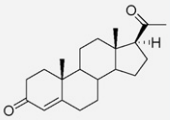
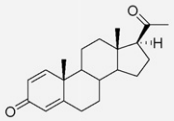
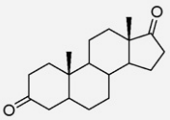
2.8. 17-Propionyloxy-androsta-1,4-diene-3-one (**2g**)

Mp. 136–137 °C; $[\alpha]_D^{20}$ 33° (c 0.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.87 (s, 3H), 1.03–1.10 (m, 3H), 1.14 (t, J = 7.5 Hz, 3H), 1.22 (s, 3H), 1.33–1.42 (m, 1H), 1.46–1.54 (m, 1H), 1.61–1.83 (m, 6H), 1.94 (m, 1H), 2.15–2.22 (m, 1H), 2.31 (q, J = 7.5 Hz, 2H), 2.33–2.50 (m, 2H), 4.60 (t, J = 8.0 Hz, 1H), 6.07 (t, J = 1.5 Hz, 1H), 6.21 (dd, J = 2.0, 10.0 Hz, 1H), 7.06 (d, J = 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 9.3, 12.1, 18.8, 22.4, 23.7, 27.5, 27.8, 32.7, 33.1, 35.9, 36.6, 43.5, 50.0, 52.2, 82.1, 124.0, 127.6, 155.6, 168.8, 174.4, 186.2; MS (EI): m/z 342 (M^+, 3%), 122 (100%); Anal. calcd. for $C_{22}H_{30}O_3$: C, 77.16; H, 8.83. Found: C, 76.92; H, 8.84.

2.9. Pregna-1,4-diene-3,20-dione (**2h**)

Mp 149–150 °C; $[\alpha]_D^{20}$ 121° (c 0.89, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.70 (s, 3H), 1.02–1.19 (m, 3H), 1.23 (s, 3H), 1.26–1.30 (m, 1H), 1.40–1.48 (m, 1H), 1.62–1.75 (m, 4H), 1.77–1.82 (m, 1H), 1.94–1.99 (m, 1H), 2.06–2.10 (m, 1H), 2.12 (s, 3H), 2.13–2.22 (m,

Table 2
Δ^1-Dehydrogenation of Δ^4-3-keto-steroids with DDQ in the presence of TBDMSCl.

Entry	Reactant	Product	Time	Yield[a]	Entry	Reactant	Product	Time	Yield[a]
1	 **1b**	 **2b**	48 h	78%	5	 **1f**	 **2f**	64 h	30.2
2	 **1c**	 **2c**	40 h	74%	6	 **1g**	 **2g**	36 h	81%
3	 **1d**	 **2d**	36 h	69%	7	 **1h**	 **2h**	40 h	75%
4	 **1e**	 **2e**	24 h	85%	8	 **1i**		48 h	NR

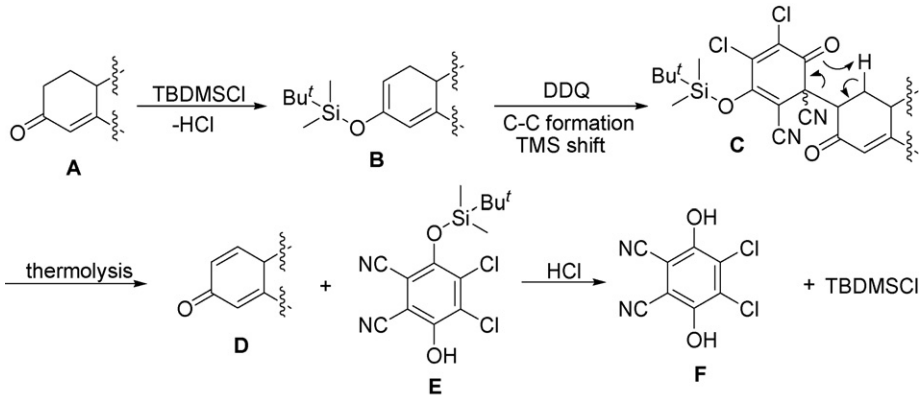
[a] Isolated yield by crystallization.

1H), 2.35–2.40 (m, 1H), 2.43–2.53 (m, 2H), 6.08 (t, J = 1.2 Hz, 1H), 6.45 (dd, J = 1.6, 8.0 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 13.4, 18.7, 22.7, 22.8, 24.5, 31.4, 32.7, 33.5, 35.5, 38.5, 43.5, 44.1, 52.2, 55.6, 63.4, 123.9, 127.5, 155.6, 168.9, 186.3, 209.1; MS (EI): m/z 312 (M^+, 5%), 122 (100%); Anal. calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.54; H, 9.12.

3. Results and discussion

To explore this process, we selected 4-androsten-3,17-dione **1a** (AD) as substrate for reaction development and screened several chlorosilane agents in common solvents for their catalytic activity. When AD and DDQ were reacted in the presence of 5 mol% $(CH_3)_3SiCl$ in dioxane at room temperature, a conversion of AD was obtained with a 3:1 Δ^1/Δ^5 dehydrogenation ratio (Table 1, entry 4). Additionally, solvents such as benzene and chloroform were not effective as dioxane. In the absence of silylating agent, the 1,2-dehydrogenation cannot occur at room temperature. We then examined several silylating agents and found tertbutyldimethylchlorosilane to be the most effective catalyst with high conversion and regioselectivity (entry 7). Further optimization showed that the addition of DDQ at 0 °C then allowing the temperature of the reaction mixture to warm to room temperature could give 92.7% conversion as well as a 95:5 Δ^1/Δ^5 dehydrogenation ratio (entry 11). After simple workup and crystallization, the desired pure product could be obtained in 75.2% yield.

The optimized protocol was further applied to six Δ^4-3-keto-steroids, and the corresponding Δ^1-dehydrogenation products were isolated in gram quantities with moderate to good yields ranging from 69% to 81% (Table 2, entries 1–3, 6 and 7) except



Scheme 1.

for 6-methylene-4-androstene-3,17-dione (entry 5) [17]. It is also noteworthy to mention that the nonsteroidal enone could be dehydrogenated with DDQ at room temperature catalyzed by TBDMSCl (entry 4). The present method was chemoselective and 3-keto-steroid for example androstan-3,17-dione cannot occur dehydrogenation under this condition (entry 8).

On the basis of report on the reaction of silyl enol ethers [18,19], a plausible reaction mechanism is shown in Scheme 1. Treatment of Δ^1-3-keto-steroid with chlorosilane could produce **B** which later reacts with DDQ to give the adduct **C**. Thermolysis of adduct **C** led to the formation of the desired $\Delta^{1,4}$-3-keto-steroid and hydroquinone silyl ether **E**, which was transformed into chlorosilane and hydroquinone **F** in the presence of HCl (Scheme 1).

In summary, we have developed a mild and efficient synthesis of $\Delta^{1,4}$-3-keto-steroids. Addition of the chlorosilane agent could greatly promote the reactivity and regioselectivity in the DDQ dehydrogenation of Δ^4-3-keto-steroids at room temperature. Further studies to extend the reaction to more functionalized steroids are now in progress in our laboratory.

Acknowledgements

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