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A concise effective deprotection of spiro 3-cyclic thiaza ketal of steroidal 1,4-dien-3-one

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ARTICLE INFO

Article history:
Received 19 June 2006
Received in revised form
21 October 2006
Accepted 25 October 2006
Published on line 4 December 2006

Keywords:
1,4-Dien-3-one steroids
Carbonyl protection
Deprotection
2-(Methylamino)benzethiol

ABSTRACT

An effective deprotective method of spiro 3-cyclic thiaza ketal of steroidal 1,4-dien-3-ones using alkyl vinyl ether in the presence of protic acid followed by the treatment of aqueous alkali was described. This novel protocol could be fulfilled under mild condition with high yield. The mechanism mediated by a carbonium ion formed *in situ* was clarified by the capture of the cleaved fragment.

1. Introduction

Since the androsta-1,4-dien-3,17-dione (**ADD**) is available from the microbial degradation of natural sterols at manufacturing scale, many efforts on exploring synthetic method of diverse steroidal compounds from **ADD**, particularly those drugs with the same A ring moiety, have been made [1–3]. In structural modification, the 1,4-dien-3-one should be protected in some reactions because this cross-conjugated system is very labile to strong acidic or basic condition and may suffer nucleophilic attack of agents such as metal hydrides, organic metallic reagents and so on [4,5]. However, there is lack of an appropriate protective method for the 3-carbonyl group of this sensitive A ring. Müller et al. reported that the 3-one of **ADD** could be regioselectively protected by reaction with 2-(methylamino)benzethiol in the presence of BF_3 to give 3′-methylspiro[androsta-1,4-dien-3,2′(3′H)benzothiazol]-17-one (**1**) in good yield, apparently as a mixture of diastereomers at the spiro ketal center [6] (Fig. 1). It is likely that this protecting group can tolerate those reaction conditions and reagents mentioned above. We have expanded this method to protect a series of steroidal compounds containing 1,4-dien-3-one with satisfactory results [7]. Unfortunately, the protected group is quite stable and difficult to deprotect. According to our knowledge, up till now, the deprotection of this spiro benzothiazolidine ketal of steroidal 1,4-dien-3-ones has not been reported in literature.

Chikashita et al. reported a few deprotective methods in non-steroidal substrates using $AgNO_3$, $HgCl_2$, NBS and Chloramine T as the reagents [8]. But $AgNO_3$ and $HgCl_2$ are not suitable for commercial-scale application owing to their high cost or toxicity. The yield of deprotection with Chloramine T is unsatisfactory. We repeated the Chikashita's method with NBS on our protected steroids and this resulted in low yield of the deprotective products.

Hereby, we would like to report a new, effective deprotective protocol of spiro 3-cyclic thiaza ketal of steroidal 1,4-dien-3-ones using alkyl vinyl ether in the presence of protic acid

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doi:10.1016/j.steroids.2006.10.008

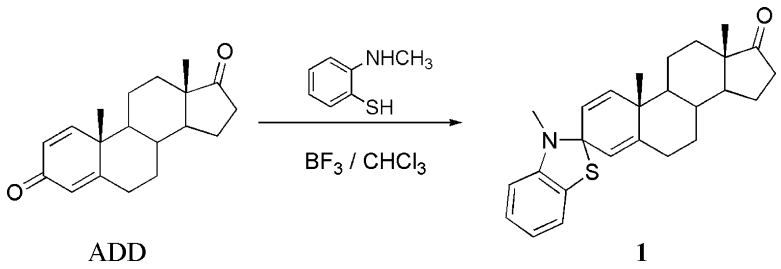


Fig. 1 – Synthesis of compound (1).

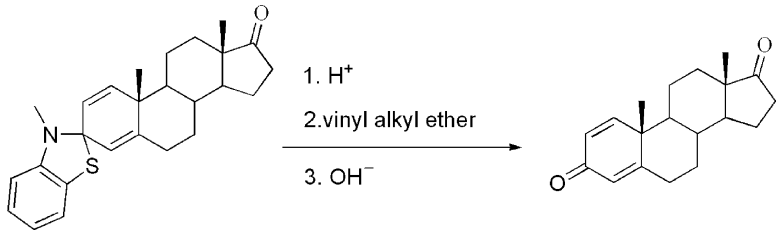


Fig. 2 – The deprotective method for spiro 3-cyclic thioaza ketal of steroidal 1,4-dien-3-one.

followed by the treatment of aqueous alkali. An example is shown in Fig. 2. This method could be completed by stirring the reaction mixture under room temperature for a short period with high yield (Table 1).

2. Experimental

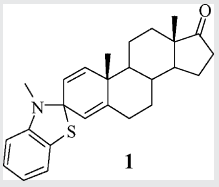
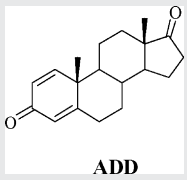
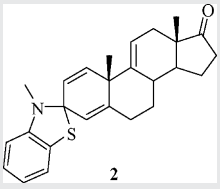
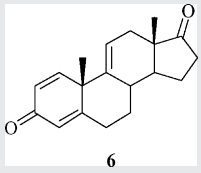
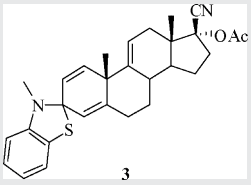
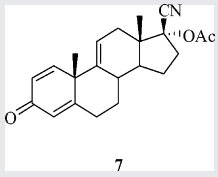
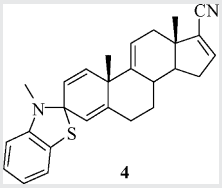
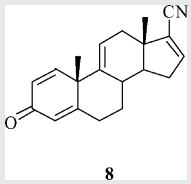
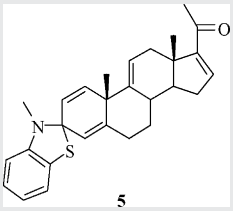
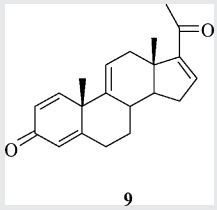
All reagents and solvents used were of analytical grade. All reactions were monitored by TLC (silica H, petroleum ether/ethyl acetate, 5:1 (v/v)). Melting points were determined in open capillary tubes and were uncorrected. ^{1}H NMR spectra were recorded in a Brucker-DPX 300, 400 and 500 MHz spectrometer in $CDCl_3$. ^{13}C NMR spectra were recorded in a Varian-Mercury Plus 400 MHz spectrometer in $CDCl_3$. Mass spectra were measured with HP5973N, HP5989A analytical mass spectrometers and Agilent LC/MSD. IR spectra were recorded in a Micolet AVATAR 360 FT-IR spectrometer.

2.1. *The typical protective procedure*

2.1.1. Synthesis of 3′-methylspiro[androsta-1,4-dien-3,2′(3′H)benzothiazol]-17-one (1) was according to reference [6]

2.1.1.1. Synthesis of 3′-methylspiro[androsta-1,4-dien-3,2′(3′H) benzothiazol]-9(11),16-dien-17-nitrile (4). 17-Cyanoandrosta-1,4,9(11),16-tetraen-3-one (**8**) (7.05 g, 24.21 mmol) was dissolved in 100 mL chloroform and 0.2 mL of $BF_3{\cdot}Et_2O$ was added. Then, freshly prepared 2-(methylamino)-benzenethiol (3.52 g, 25.29 mmol) was added dropwise. The mixture was stirred for 7 h at reflux, cooled to room temperature, washed with water, extracted with chloroform, and dried over Na_2SO_4. After filtration, removal of the solvent gave a yellow oil. This oil was purified by silica column chromatography with ethyl acetate/petroleum (1:17) as the eluent to afford the title compound. Yield: 5.66 g (57%).

Table 1 – Deprotection of spiro 3-cyclic thiaza ketal of steroidal 1,4-dien-3-ones

Substrates	Products	Yield (%)
		93
		90
		91
		88
		80

2.2. The typical deprotective procedure

2.2.1. Deprotection of 3′-methylspiro[androsta-1,4-dien-3,2′(3′H)benzothiazol]-17-one (1)

pTSA (201 mg, 1.06 mmol) and ethyl vinyl ether (763 mg, 10.6 mmol) were added to a solution of 3′-methylspiro-[androsta-1,4-dien-3,2′(3′H)benzothiazol]-17-one (**1**) (430 mg, 1.06 mmol) in 10 mL THF. The mixture was stirred at room temperature for 15 min, then washed with aqueous Na_2CO_3, extracted with chloroform (30 mL ×3), and dried over Na_2SO_4. After filtration, removal of the solvent gave a yellow oil. This oil was purified by silica column chromatography by elution with ethyl acetate/petroleum (1:100) to afford 2-(1-ethoxyethylthio)-*N*-methylbenzeneamine (**10**) (152 mg) in 68% yield, and by elution with ethyl acetate/petroleum (1:1) to afford androsta-1,4-dien-3,17-dione (280 mg) in 93% yield.

2.2.2. Deprotection of 3′-methylspiro[androsta-1,4-dien-3,2′(3′H)benzothiazol]-9(11),16-dien-17-nitrile (4)

pTSA (201 mg, 1.06 mmol) and ethyl vinyl ether (763 mg, 10.6 mmol) were added to a solution of 3′-methylspiro[androsta-1,4-dien-3,2′(3′H)benzothiazol]-9(11),16-dien-17-nitrile (**4**) (437 mg, 1.06 mmol) in 10 mL THF. The mixture was stirred at room temperature for 15 min, then washed with aqueous Na_2CO_3, extracted with chloroform (30 mL ×3), and dried over Na_2SO_4. After filtration, removal of the solvent gave a yellow oil. This oil was purified by silica column chromatography by elution with ethyl acetate/petroleum (1:100) to afford 2-(1-ethoxyethylthio)-*N*-methylbenzeneamine (**10**) (138 mg) in 62% yield, and by elution with ethyl acetate/petroleum (1:1) to afford 17-cyanoandrosta-1,4,9(11),16-tetraen-3-one (**8**) (271 mg) in 88% yield.

2.3. Analytical and spectroscopic data of compounds

2.3.1. 3′-Methylspiro[androsta-1,4-dien-3,2′(3′H)benzothiazol]-9(11), 16-dien-17-nitrile (4)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.90 (3H, s, 18-CH_3), 0.96–2.61 (10H, m, steroidal skeleton saturated H), 1.30 (3H, s, 19-CH_3), 2.56 (3H, s, –N(CH_3)), 5.52 (1H, d, J = 5.5 Hz, 11-H), 5.73 (1H, s, 4-H), 6.02–6.13 (2H, m, arom-H), 6.29 (1H, t, J = 6.9 Hz, 2-H), 6.64–6.68 (2H, m, 1-H and 16-H), 6.98 (2H, m, arom-H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 147.2; 146.7; 145.8; 145.2; 136.4; 125.7; 124.7; 124.2; 121.5; 119.0; 118.7; 117.6; 117.2; 115.8; 107.4; 52.6; 46.8; 42.1; 42.0; 36.4; 34.8; 34.7; 33.9; 33.5; 31.1; 30.3; 27.7; MS (*m*/z, %): 412 (M^+, base), 397 (M^+-CH_3, 60.72); $\nu_{(KBr)}$ (cm^{-1}): 2215 (CN), 1471 (arom), 1295 (Ar-*N*), 740 (arom); optical rotation: $[\alpha]_D^{20}$ = +187.0° ($CHCl_3$, 0.01 g/mL); mp: 157–160 °C (recrystallyzed from methanol).

2.3.2. 3′-Methylspiro[pregna-1,4-dien-3,2′(3′H)benzothiazol]-9(11),16-dien-20-one (5)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.86 (3H, s, 18-CH_3), 0.88–2.61 (10H, m, steroidal skeleton saturated H), 1.30 (3H, s, 19-CH_3), 2.28 (3H, s, 21-CH_3), 2.56 (3H, s, –N(CH_3)), 5.49 (1H, d, J = 5.9 Hz, 11-H), 5.71 (1H, s, 4-H), 6.02 (1H, m, arom-H), 6.12 (1H, t, J_1 = 10.0 Hz, J_2 = 12.6 Hz, arom-H), 6.28 (1H, t, J_1 = 7.5 Hz, J_2 = 7.9 Hz, 2-H), 6.65 (1H, t, J = 7.5 Hz, 1-H), 6.72 (1H, d, J = 3.3 Hz, 16-H), 6.97 (2H, m, J_1 = 4.4 Hz, J_2 = 7.5 Hz, arom-H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 196.5 (20-C); 153.6; 146.4; 144.9; 144.0; 136.8; 125.6; 124.7; 123.8; 121.4; 119.0 118.7; 118.5; 118.2; 107.2; 53.1; 44.4; 42.0; 41.9; 37.4; 34.6; 34.5; 34.0; 32.9; 31.2; 30.3; 27.7; 27.0; MS (*m*/z, %): 430 (M + 1, 86.02), 415 (M-CH_3, 41.65), 43 (Ac-, base): $\nu_{(KBr)}$ (cm^{-1}): 1660 (C=O), 1474 (arom), 1299 (Ar-N), 738 (arom); optical rotation: $[\alpha]_D^{20}$ = +188.4° ($CHCl_3$, 0.01 g/mL); mp: 203–206 °C (recrystallyzed from ethyl acetate).

2.3.3. 17α-Acetoxy-17β-cyanoandrosta-1,4,9(11)-trien-3-one (7)

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.06 (3H, s, 18-CH_3), 1.16–2.69 (12H, m, steroidal skeleton saturated H), 1.44 (3H, s, 19-CH_3), 2.08 (3H, s, –C(O)CH_3), 5.62 (1H, d, J = 5.7 Hz, 11-H), 6.09 (1H, s, 4-H), 6.30 (1H, dd, J_1 = 1.3 Hz, J_2 = 10.2 Hz, 2-H), 7.21 (1H, d, J = 10.2 Hz, 1-H); MS (*m*/z, %): 352 (M^+ + 1, 6.76), 351 (M^+, 6.16), 43 (AcO, base); mp: 204–206 °C (recrystallyzed from methanol).

2.3.4. 17-Cyanoandrosta-1,4,9(11),16-tetraen-3-one (8)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.85–2.71 (10H, m, steroidal skeleton saturated H), 0.95 (3H, s, 18-CH_3), 1.44 (3H, s, 19-CH_3), 5.60 (1H, s, 11-H), 6.09 (1H, s, 4-H), 6.30 (1H, dd, J_1 = 1.8 Hz, J_2 = 10.3 Hz, 2-H), 6.66 (1H, s, 16-H), 7.21 (1H, d, J = 10.3 Hz, 1-H); MS (*m*/z, %): 291(M^+, 29.14), 149 (base); mp: 138–140 °C (recrystallyzed from ethyl acetate).

2.3.5. 2-(1-Ethoxyethylthio)-N-methylbenzeneamine (10)

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.21 (3H, t, J = 7.1 Hz, –OCH_2CH_3), 1.44 (3H, d, J = 6.3 Hz, S-CH(CH_3)-O), 2.87 (3H, s, NCH_3), 3.47 (1H, m, –OCH_2CH_3), 3.93 (1H, m, –OCH_2CH_3), 4.74 (1H, q, J_1 = 6.3 Hz, J_2 = 12.4 Hz, S-CH(CH_3)-O), 5.21 (1H, br, NH), 6.61 (2H, q, J_1 = 7.2 Hz, J_2 = 7.4 Hz, arom-H), 7.24 (1H, t, J = 7.3 Hz, arom-H), 7.35 (1H, d, J = 7.6 Hz, arom-H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 14.943 (-OCH_2CH_3), 22.517 (S-CH(CH_3)-O), 30.432 (NCH_3), 64.202 (-OCH_2CH_3), 85.131 (S-CH(CH_3)-O), 109.457 (arom-c), 114.601 (arom-c), 116.337 (arom-c), 130.431 (arom-c), 137.493 (arom-c), 151.101 (arom-c); MS (*m*/z, %): 211 (M^+, 2.86), 139 (M^+-CH_2-CH-OCH_2CH_3, 40.11), 43 (CH_3CH_2O-, base); $\nu_{(KBr)}$ (cm^{-1}): 3388 (Ar-NH); optical rotation: $[\alpha]_D^{20}$ = +0.07° ($CHCl_3$, 0.027 g/mL). Colorless liquid.

The proton NMR, IR and MS data of androsta-1,4,9(11)-trien-3,17-dione (**6**) and pregna-1,4,9(11), 16-tetraen-3,20-dione (**9**) agreed well with the literature value. Androsta-1,4,9(11)-trien-3,17-dione (**6**), mp: 166–167 °C (Lit. [9], mp: 167–169 °C). Pregna-1,4,9(11),16-tetraen-3,20-dione (**9**), mp: 206–208 °C (Lit. [10], mp: 204–208 °C).

3. Results and discussion

We applied this method on the 3-protected substrates (**1–5**) and got the corresponding 3-deprotected products **ADD**, (**6–9**) in excellent yields. As experiments show, this deprotective method has a high chemo-selectivity, and the cyano, ester groups and double bond in substrates are not attacked.

In our method, the alkyl vinyl ethers could be ethyl vinyl ether, butyl vinyl ether and 3,4-dihydro-2H-pyran. However, the reaction rate with ethyl vinyl ether and butyl vinyl ether as deprotective agents is quite similar and fast (about 15–30 min). But when 2H-pyran was used as the deprotective agent, the reaction rate was much slower (the completion of reaction could be lasted up to 5 h). The protic acids using in our method

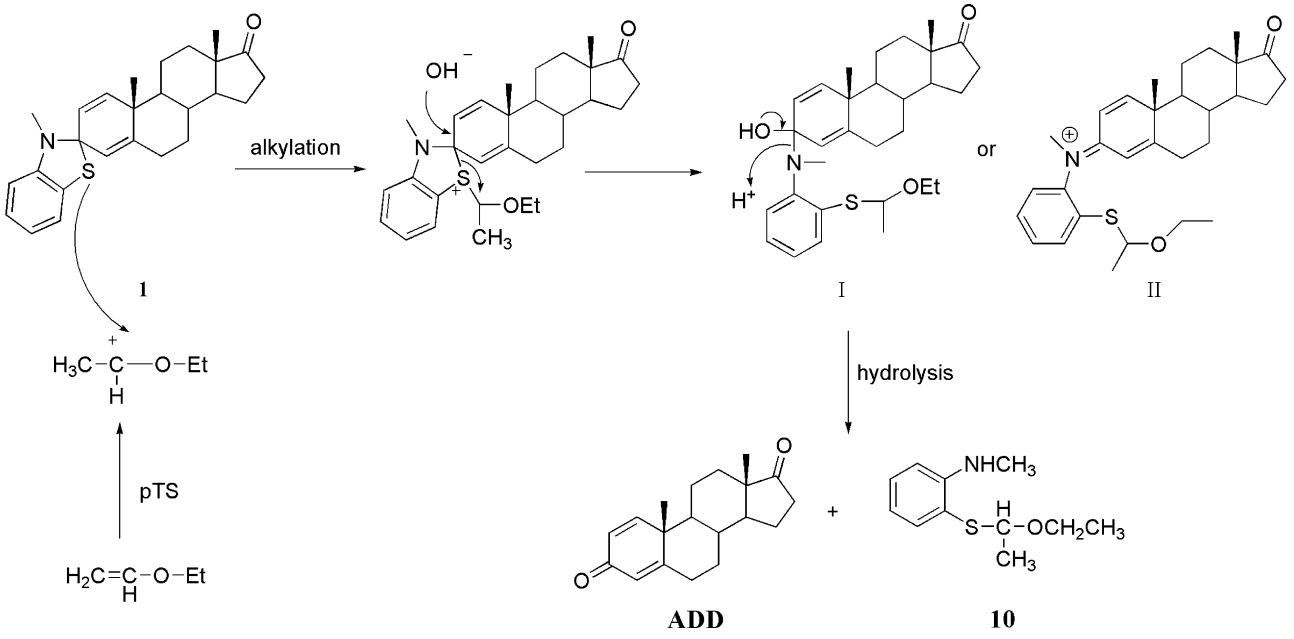


Fig. 3 – The suggested mechanism for deprotection.

could be pTSA. Anhydrous HCl also could be used in this deprotection procedure instead of pTSA; all data of the reaction was just the same as that with pTSA as catalyst, including the reaction conditions, work-up procedure and yields.

A reasonable mechanism was depicted in Fig. 3. At first, the sulfur or nitrogen atom in thiaza ketal was alkylated by the carbonium ion formed *in situ* which weakened the bond between hetero atom and 3-carbon. The alkylated intermediate became easy to be cleaved by hydrolysis and 1,4-dien-3-one was regenerated. The first alkylation that occurred at the sulfur atom was clarified by the capture of compound (**10**). In order to illustrate this deprotection whether via the intermediate I or iminium intermediate II, we examined the reaction details with compound (**1**) as substrate. Before hydrolysis, the removal of all the solvent and the excess ethyl vinyl ether give an oil residue, ^{1}H NMR spectra of which showed there was no iminium characterization because the chemical shift of methyl on nitrogen (δ 2.29) was similar to that of the starting protected substrate. There did not seem to be a methyl on the iminium nitrogen.

In conclusion, we discovered a novel practical deprotective procedure for the spiro 3-cyclic thiaza ketal of steroidal 1,4-dien-3-ones. In addition to its selectivity, the low cost and availability of the reagents, mild reaction condition, simplicity of the work-up procedure, short reaction time and excellent yields can also be considered as strong advantages of this method. Due to the exploration of this simple deprotective method, the application of 2-(methylamino)benzethiol as a protective reagent for the 1,4-dien-3-one of steroids will become a feasible synthetic strategy, and we believe the expansion of this method will offer great benefit in organic synthesis.

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