Iodine-promoted cleavage of the C-17-dihydroxyacetone side chain of corticosteroids in aqueous ammonia water

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A convenient approach to 17-ketosteroids by the iodine-promoted cleavage of the C-17-dihydroxy acetone side chain of corticosteroids is described. Treatment of steroids containing the C-17-dihydroxyacetone side chain with iodine and an excess of aqueous ammonia in acetonitrile at 50 °C, affords high yields of the corresponding 17-ketosteroids.

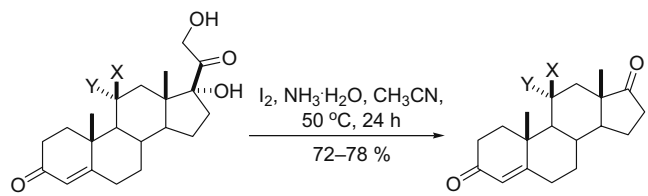
Keywords: corticosteroids, 17-ketosteroids, molecular iodine, cleavage reaction

17-Ketosteroids and corticosteroids bearing a C-17-dihydroxyacetone side chain are some of the most important compounds in steroid chemistry.[1,2] The degradation of steroids having the two-carbon side chain at the 17-position is an important reaction because the products play an important role as key intermediates in the biological conversion of steroidal hormones.[3-5] These reactions have therefore attracted considerable attention. Various methods for the chemical transformation of corticosteroids to form 17-ketosteroids have been reported.[6-12] These reactions are normally carried out in the presence of a strong base or by using oxidative methods. Although earlier reactions for the transformation of corticosteroids to form 17-ketosteroids are still considered to be useful, they require harsh reaction conditions and the yields are often unsatisfactory. Recently a new simple and elegant transformation of corticosteroids to form 17-ketosteroids has been described.[6] The procedure used sodium methoxide as a strong base which attacked the C-17-dihydroxyacetone side. The development of new approaches using mild reaction conditions is an active research field. Recently iodine has been used as a mild promoter for various organic transformations to afford the products in excellent yields with high selectivity. It has also been reported to be a mild, cheap and easily available oxidising reagent and is less toxic than molecular bromine or chlorine. Iodine has been explored as a powerful catalyst for various organic transformations.[13-16] To our knowledge, there are no reports of the iodine-promoted cleavage of the C-17-dihydroxyacetone side chain of corticosteroids in aqueous ammonia. In continuation of our studies with molecular iodine mediated reactions, we reasoned that iodine might be used to effect the C–C bond cleavage reactions of corticosteroids in the presence of aqueous ammonia. We report here a novel chemical transformation of corticosteroids bearing a C-17-dihydroxyacetone side chain to afford 17-ketosteroids promoted by molecular iodine under ambient conditions with excellent yields. Scheme 1.

Results and discussion

In our initial work, based on the classical method using a base as a catalyst, 11β,17,21-trihydroxy-pregn-4-ene-3,20-dione **1a** and 35% aqueous ammonia were stirred at room temperature in CH_3CN in the absence of iodine. After 24 hours, only 10% of the starting material was consumed; then at elevated temperature 50 °C, only 18% of product **2a** was obtained after workup of the reaction after the same reaction time. To improve the product yields and to optimise the reaction conditions, iodine was used in an equiomolar amount. The reaction was carried out under similar conditions. To our surprise, a significant improvement in the yield of the product **2a** (64% in yield) was observed. Encouraged by these results, we investigated the reaction further using different amounts of iodine. The increase in the quantity of iodine from 1.0 to 1.5 equiomolar enhanced the product yield from 64 to 72%. We varied the solvent and found that acetonitrile gave the best result. We found that CH_3CN, DMF, THF, or DMSO gave the product **2a** in yield at 72%, 50%, 59% and 31% respectively. Furthermore, faster reaction occurred on increasing the temperature from room temperature to 50 °C and the reaction time was reduced to 24 h. In order to evaluate the efficiency of iodine as a promoter, the reactants **1a–c** were treated with ammonia in the presence of 1.5 equiomolar of iodine to generate product **2a–c**. The results are summarised in Scheme 1.

The products **2a–c** were fully characterised by spectroscopic analysis. The IR spectra of the products showed C_{17}=O stretching band at 1736–1740 cm^{-1} and C_3=O stretching in



1a–c **2a–c**

Entry	X	Y	17-Ketosteroids (**2**)(%)
a	HO	H	72
b	H	H	78
c	-O-		76

Scheme 1

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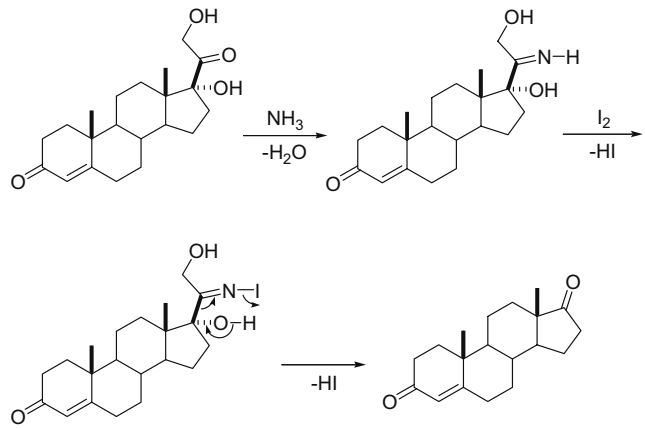

Scheme 2 Plausible reaction pathway for cleavage of the side chain of corticosteroids

the band at 1654–1672 cm^{-1}. ^1H NMR spectra, C_4-alkene proton was observed as singlet at 5.69–5.75 ppm. The protons belonging to α-methylene adjacent to the carbonyls were observed within the expected chemical shift values.

The mechanism for the conversion of the corticosteroids to 17-ketosteroids can be tentatively explained as shown in Scheme 2. An imine is first formed by nucleophilic addition of ammonia to the 20-carbonyl, followed by iodo-substitution in nitrogen of the imine and the efficient cleavage of C17–C20 bond.[17]

In conclusion, we have successfully developed an easy and efficient method to prepare a variety of 17-ketosteroids by the reaction of different corticosteroids with ammonia in the presence of 1.5 equiomolar of iodine at 50 °C. The promoting activity of iodine is remarkable and affords an environmentally benign process.

Experimental

Elemental analytical data were obtained by using a model 240 analytical instrument, IR spectra were measured with a model 408 infrared spectrometer, ^1H NMR and ^{13}C NMR spectra were recorded on a JNM-90Q spectrometer by using TMS as an internal standard ($CDCl_3$ as solvent).

Procedure for cleavage of the C-17-dihydroxyacetone side chain of corticosteroids using molecular iodine

A mixture of 11β,17,21-trihydroxypregn-4-ene-3,20-dione (**1a**; 182 mg, 0.5 mmol), Iodine (190 mg, 0.75 mmol) and 35% aqueous ammonia (3.5 ml) in CH_3CN (15 ml) was stirred at 50 °C for 24 h. After TLC showed the starting material disappeared, the mixture was extracted with CH_2Cl_2 (30 ml). The CH_2Cl_2 layer was washed with water, 10% $Na_2S_2O_3$, water and brine, and dried over Na_2SO_4. The product was purified by column chromagraphy (silica gel, EtOAc/hexanes/MeOH, 1/1/0.1) to give 11β-hydroxy-4-androstene-3,17-dione (**2a**; 110 mg, 72% yield) as white crystals: m.p. 192–194 °C (EtOAc–hexanes) (lit.[6]: 188–190 °C); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.69 (s, 1H), 4.46 (m, 1H), 1.48 (s, 3H), 1.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 219.0, 199.2, 171.7, 122.2, 67.5, 56.5, 52.2, 46.6, 40.6, 39.2, 35.1, 34.7, 33.6, 31.7, 31.4, 30.8, 21.5, 20.8, 15.6; IR (KBr, cm^{-1}): ν 3414, 1736, 1654, 1447. Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67; Found: C, 75.19; H, 8.82%.

4-Androstene-3,17-dione (**2b**): 78% yield; white crystals, m.p. 170.5–172 °C (EtOAc–hexanes) (lit.[6]: 169–171 °C); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.75 (d, J = 0.3 Hz, 1H), 1.22 (s, 3H), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 220.2, 199.2, 170.3, 124.2, 53.9, 51.0, 47.6, 38.7, 35.8(2C), 35.3, 34.0, 32.7, 31.4, 30.9, 21.8, 20.4, 17.5, 13.8; IR (KBr, cm^{-1}): ν 1740, 1672, 1448. Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15; Found: C, 79.44; H, 9.32%.

4-Androstene-3,11,17-trione (**2c**): 76% yield; white crystals, m.p. 218–220 °C (EtOAc–hexanes) (lit.[6]: 218–220 °C); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.74 (s, 1H), 1.44 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 216.7, 207.5, 199.4, 167.8, 124.9, 63.4, 50.5, 50.4, 49.9, 38.4, 36.4, 36.0, 34.8, 33.8, 32.1, 31.0, 21.6, 17.4, 14.7; IR (KBr, cm^{-1}): ν 1740, 1702, 1665, 1447. Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05; Found: C, 75.69; H, 8.33%.

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References

1 T. Miura, K. Yamauchi, H. Takahashi and Y. Nagahama, *Proc. Natl. Acad. Sci.* USA, 1991, **88**, 5774.
2 E.-E. Baulieu, *Biol. Cell* 1991, **71**, 3.
3 E.P. Oliveto, Synthesis and degradation of the pregnane side-chain. In: J. Fried and J.A. Edwards; (eds), Organic reactions in steroid chemistry, Vol. 2. Van Nostrand Reinhold Co., New York, pp. 127-236, 1972.
4 M.L. Di Gioia, A. Leggio, A. Le Pera, A. Liguori, A. Napoli and C. Siciliano, *Tetrahedron Lett.,* 2001, **42**, 7413.
5 C.J. Singer, F. Iohan and C. Monder, *Endocrinology*, 1986, **119**, 1356.
6 A.L. Pera, A. Leggio, C. Siciliano, M.L. Di Gioia, A. Napoli, G. Sindona and A. Liguori, *Steroids*, 2003, **68**, 139.
7 T.M. Lockman, J.L. Irwin, L.F. Blackwell, P.S. Davie, M. Thomas and G. Young, *Steroids,* 1997, **62**, 655.
8 S. Sato, M. Nakada and M. Shibasaki, *Tetrahedron Lett.,* 1996, **37**, 6141.
9 Q. Zhao and Z. Li, *Steroids,* 1994, **59**, 190.
10 Y. Horiguchi, E. Nakamura and I. Kuwajima, *J. Am. Chem. Soc.,* 1989, **111**, 6257.
11 Jr. S.S. Simons, M.J. Merchlisky and D.F. Johnson, *Steroids,* 1981, **37**, 281.
12 F. Ungar and R. Dorfman, *J. Am. Chem. Soc.,* 1954, **76**, 1197.
13 J.S. Yadav, P.K. Chand and S. Anjaneyulu, *Tetrahedron Lett.,* 2002, **43**, 3783.
14 B. Ke, Y. Qin, Q. He, Z. Huang and F. Wang, *Tetrahedron Lett.,* 2005, **46**, 1751.
15 B.K. Banik, M. Fernandez and C. Alvarez, *Tetrahedron Lett.,* 2005, **46**, 2479.
16 B.K. Banik, O. Zegrocka and F.F. Becker, *J. Chem. Res. (S)* 2000, 321.
17 N. Mori and H. Togo, *Synlett*, 2005, 1456.