Oxidative Cleavage of 1,3-Dicarbonyls to Carboxylic Acids with Oxone

Scott W. Ashford* and Kevin C. Grega

Chemical Process Research and Development, 1500-91-201, Pharmacia, Kalamazoo, Michigan 49001

scott.w.ashford@pharmacia.com

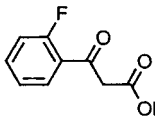
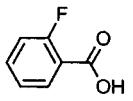
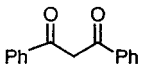
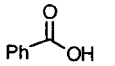
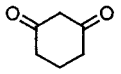
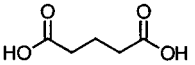
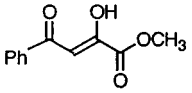
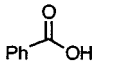
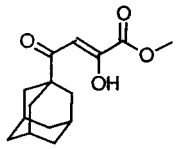
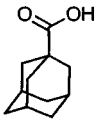
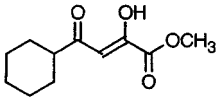
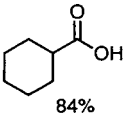
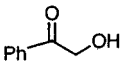
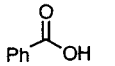
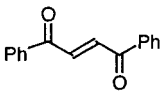
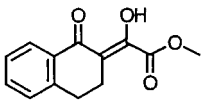
Received November 6, 2000

In response to potential market demand for 17-β carboxysteroids, a research program to develop a commercial process to prepare androst-4-ene-17-β-carboxylic acid (AD-Acid) **4** was initiated. Progesterone **1**, was logically chosen as our starting material due to its structural similarity to the desired product, availability, and favorable cost. The desired transformation required that the terminal methyl ketone be converted to a carboxylic acid. The most well-known method to affect this transformation, the haloform reaction,[1] involves iterative halogenation at the enolizable carbon and subsequent hydrolysis under very basic conditions to generate the carboxylic acid. Unfortunately, base-sensitive substrates or those that are susceptible to halogenation do not tolerate these reaction conditions. In particular, attempts to apply the haloform chemistry to progesterone did not produce an acceptable commercial process due to competitive bromination of the A-ring. An alternative approach would involve oxidation α to the carbonyl (Rubottom oxidation[2] or oxaziridine hydroxylation[3]) followed by oxidative cleavage to produce the desired acid. However, these methods were not successful when applied to our substrate. As an alternative to the existing methodology, we wish to report a mild two-step process for converting progesterone **1** to AD-Acid **4** and, more generally, a one-step method for converting 1,3-dicarbonyl compounds to carboxylic acids (Scheme 1).

After many unsuccessful attempts to directly oxidize the methyl ketone of progesterone, we decided to explore the oxidative degradation of **3**. Encouraged by literature precedence for the hydroxylation of 1,3-dicarbonyl compounds with dimethyldioxirane to form 2-hydroxyl-1,3-dicarbonyls,[4] we speculated that the enol tautomer **3** would be susceptible to oxidation and ultimately to oxidative cleavage to yield the requisite carboxylic acid. In the example of progesterone, it was necessary to differentiate the two carbonyls for regioselective control in the diethyl oxalate condensation reaction. This was accomplished through selective protection of the A-ring enone as the methyl enol ether by reacting **1** with trimethylorthoformate and *p*-TSA in methanol to obtain **2** in 79% yield. Intermediate **3** was obtained in 85% yield after condensation with diethyl oxalate in the presence of sodium methoxide.[5] To avoid the arduous preparation of dimethyldioxirane, we opted to use methyl(trifluoromethyl)dioxirane generated in situ in acetonitrile with Oxone[6] and trifluoroacetone.[7] Surprisingly, AD-Acid **4** was obtained directly when a mixture of **3**, $Ni(acac)_2$, trifluoroacetone, and $NaHCO_3$ in acetonitrile was treated with an aqueous solution of Oxone.

Further experimentation revealed that the oxidative degradation occurred when a mixture of **3** and $NaHCO_3$ in acetonitrile or acetone was simply treated with an aqueous solution of Oxone.[8] We have determined that,

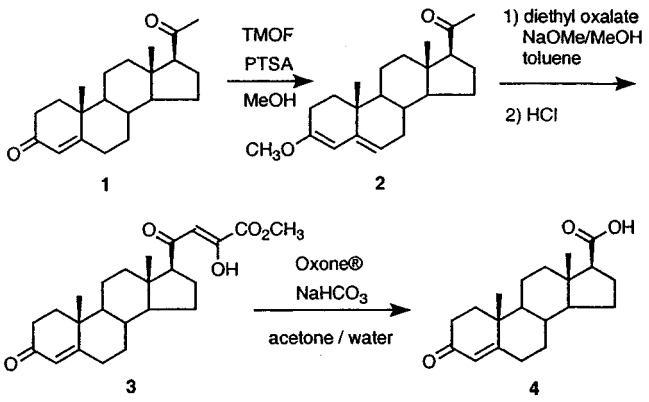
Table 1. Oxidative Cleavage of Different Functional Groups with Oxone to Generate Carboxylic Acids

Entry	Substrate	Product/yield
1		 90%
2		 97%
3		 14%
4		 96%
5		 93%
6		 84%
7		 93%
8		83 % recovered starting material
9		85 % recovered starting material
10		Does not cleave to acid

(1) Fusan, R. C.; Bull, B. A. *Chem. Rev.* **1934**, *15*, 275.
(2) Rubottom, G. M.; Gruber, J. M.; Juve, H. D., Jr.; Charleson, D. A. *Org. Synth.* **1985**, *64*, 118−125.
(3) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*(18), 5703−42.
(4) Adam, W.; Smerz, A. K. *Tetrahedron* **1996**, *52*, 5799−5804.
(5) McCombs, C. A. U. S. Patent 81-239799, 1982.
(6) Oxone: $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$.
(7) Yang, D.; Wong, M.; Yip, Y. *J. Org. Chem.* **1995**, *60*, 3887−3889.

10.1021/jo001579m CCC: $20.00
Published on Web 01/19/2001

Scheme 1



for optimum reaction, a base is required to buffer the system to prevent the decomposition of the potassium peroxymonosulfate which occurs at low pH (<5).[9] If conducted in the absence of base, the reaction stalls as the pH drops during the Oxone addition.

Our preliminary results show this reaction to be general to 1,3-dicarbonyl compounds and α-hydroxy ketones as indicated by the examples in Table 1.[10] Oxalate derivatives (entries 4−6) as well as simple malonic esters (entry 1) can be employed in this reaction. The reaction works equally well for aliphatic and aromatic 1,3-diketones. The simple symmetrical biaryl diketone (entry 2) undergoes clean conversion to 2 equiv of benzoic acid. The cyclic alkyl diketone (entry 3) produced the dicarboxylic acid, albeit in low yield due to isolation problems. The most interesting comparison is that of entries 7 and 8, where it is apparent that activation of the α-carbon by a simple hydroxyl group is sufficient for oxidative cleavage. Conjugated diketones (entry 9) and oxalates with alkyl substituents α to the carbonyl (entry 10) are not oxidatively cleaved.

In summary, we have developed a novel method for converting methyl ketones to carboxylic acids using Oxone to oxidatively degrade 1,3-dicarbonyl compounds and α-hydroxy ketones. This method compliments existing methodologies and is in general a milder alternative to the haloform reaction.

Experimental Section

General Methods. All reactions were conducted under an atmosphere of dry nitrogen. Solvents were used as provided from EM Science. Starting materials (Table 1, entries 1−3, 7, and 9) were purchased from Aldrich and used without purification. The starting materials of Table 1, entries 4−6 and 10, were prepared according to the general procedure described below. Structural confirmation of products was obtained by comparison to commercially available authentic material.

21-Methoxalylprogesterone (3). A solution of 3-hydroxypregna-3,5-dien-20-one-3-methyl ether (10 g, 30 mmol) in toluene (40 mL) was treated with diethyl oxalate (5.75 g, 39.3 mmol) followed by 25% NaOMe/MeOH (13.9 mL, 60.8 mmol). The solution was stirred at 35 °C for 3 h and then quenched with the addition of 1 N HCl. The organic layer was washed with water and diluted with MeOH (40 mL). The precipitated product was collected by filtration and dried under a stream of N_2 to give 21-methoxalylprogesterone as an off-white solid (10.2 g, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (s, 3 H), 1.10 (m, 3 H), 1.30 (s, 3 H), 1.51 (m, 3 H), 1.74 (m, 2 H), 1.83 (m, 2 H), 1.88 (m, 1 H), 2.13 (m, 2 H), 2.34 (m, 3 H), 2.53 (m, 4 H), 2.68 (t, 1 H), 4.0 (s, 3 H), 5.84 (s, 1 H), 6.43 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.3, 17.24, 20.77, 22.25, 24.26, 31.76, 32.62, 33.78, 35.55, 38.18, 38.46, 45.64, 52.98, 53.51, 55.91, 60.92, 102.31, 123.78, 162.60, 165.63, 199.23, 203.39.

Androst-4-ene-17-*β*-carboxylic Acid (4). A vigorously stirred mixture of 21-methoxalylprogesterone (4.0 g, 1 mmol) and $NaHCO_3$ (8.4 g, 10 mmol) in acetone (100 mL) was cooled to 0 °C. The slurry was treated with a solution of Oxone (15.4 g, 2.5 mmol) in water (60 mL) over a period of 15 min. The slurry was then warmed to 25 °C, and solid byproducts were removed by filtration. The pH of the crude product solution was adjusted between pH 4 and 5 with 1 N H_2SO_4. The product precipitated after concentration and was collected by filtration. Purification by recrystallization from a minimum volume of hot MeOH/H_2O/THF (80/20/10) gave the title compound (2.75 g, 87%) as a white crystalline solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.67 (s, 3 H), 0.91 (m, 2 H), 1.10 (m, 2 H), 1.15 (s, 3 H), 1.24 (m, 2 H), 1.40 (m, 1 H), 1.60 (m, 6 H), 1.98 (m, 3 H), 2.20 (m, 3 H), 2.40 (m, 2 H), 5.63 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 13.46, 17.21, 20.79, 23.56, 24.35, 31.99, 32.32, 33.94, 35.39, 35.51, 37.94, 38.52, 43.36, 53.53, 54.81, 55.03, 123.53, 117.09, 174.94, 198.22.

Methyl (2*Z*)-4-(1-Adamantyl)-2-hydroxy-4-oxo-2-butenoate (5). To a solution of 1-adamantyl methyl ketone (3.0 g, 16.83 mmol) in toluene (15 mL) was added diethyl oxalate (3.43 g, 25.2 mmol). After addition of a 25% $NaOCH_3$ solution (7.7 mL, 33.7 mmol), the reaction was heated at 50 °C for 5 h. CH_2Cl_2 was added and the solution washed with H_2O. The organic layer was dried over $MgSO_4$ and concentrated to a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70−1.86 (m, 12H), 2.02 (m, 3H), 3.90 (s, 3H, OCH_3), 6.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.83, 36.47, 38.38, 43.56, 53.07, 97.58, 162.84, 168.10, 207.99; HRMS calcd for $C_{15}H_{20}O_4$ 265.1440, found 265.1448.

Acknowledgment. We thank Peter G. M. Wuts for his encouragement and support in preparing this manuscript.

JO001579M

(8) Grega, K. C.; Ashford, S. W. U.S. Patent 60-159,272 1999.
(9) Zheng, T.; Richardson, D. E. *Tetrahedron Lett.* **1995**, *36*, 833−836.
(10) The adamantyl oxalate derivative (entry 5) was the only new compound prepared in this study.