Available online at www.sciencedirect.com
SCIENCE DIRECT
Journal of Molecular Catalysis A: Chemical 250 (2006) 70–74
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
www.elsevier.com/locate/molcata

Short communication

Improved chromium-catalyzed allylic oxidation of Δ^5-steroids with *t*-butyl hydroperoxide

Manolis A. Fousteris [a,b], Anna I. Koutsourea [a], Sotiris S. Nikolaropoulos [a,*], Abdelkhalek Riahi [b], Jacques Muzart [b,*]

[a] *Laboratory of Medicinal Chemistry, School of Health Sciences, Department of Pharmacy, University of Patras, 26500 Patras, Greece*
[b] *Unité Mixte de Recherche "Réactions Sélectives et Applications", Boîte no. 44, CNRS-Université de Reims Champagne-Ardenne, B.P. 1039, 51687 Reims Cedex 2, France*

Received 26 October 2005; received in revised form 2 January 2006; accepted 19 January 2006
Available online 28 February 2006

Abstract

Various chromium^{VI}-catalyzed conditions have been tested to improve the oxidation of Δ^5-steroids with *t*-BuOOH to their corresponding 5-en-7-ones. The use of PDC or the association of CrO_3 with an amine as the catalyst and CH_2Cl_2 or $PhCF_3$ as the solvent led usually to the best yields. A minor reaction pathway was the epoxidation of the double bond.

Keywords: Δ^5-Steroids; Allylic oxidation; Catalysis; Chromium oxides; *Tert*-butyl hydroperoxide

Allylic oxidation is a significant reaction in organic synthesis [1]. Among the variety of substrates, the oxidation of Δ^5-steroids to their corresponding 5-en-7-ones has attracted a particular interest since 7-keto-Δ^5-steroids are known as inhibitors of mammalian steroidal hormones biosynthesis [2] and their antiproliferative and/or cytotoxic properties render them as molecules of potent value for the cancer treatment [3] while these properties may provide sanative effects for other types of diseases [4].

The classical methods for these allylic oxidations involve the use of very large excesses (up to 40 equivalents) of chromium^{VI} reagents [5] which led to considerable amounts of toxic effluents. According to Chidambaram and Chandrasekaran [6] pyridinium dichromate (PDC) [7] independently does not effect allylic oxidation [8] while a combination of PDC and *t*-BuOOH (4 eq. of each) mediates the transformation of cholesteryl acetate (**1a**) into 3β-acetoxy-5-cholesten-7-one (**2a**) (84% conversion, 68% yield). For environmental and economical points of view, the use of only catalytic amounts of a transition metal has a greater interest. In fact, oxidations of Δ^5-steroids to corresponding 7-keto-Δ^5-steroids with *t*-BuOOH have been carried out in the presence of catalytic quantities of V [9] Cr [10–13] Mn [9,14] Fe [15] Co [9,16] Cu [9,17,18] Mo [15,19] Ru [20] and Bi [21]-based reagents. Nevertheless, the stoichiometric Cr procedures remain used nowadays [22] probably because they require solely cheap commercial reagents and led to good yields.

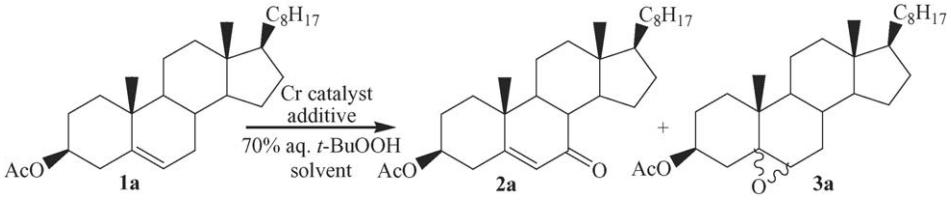
Having observed that the efficiency and the selectivity of the Cr-catalyzed oxidations of **1a** with *t*-BuOOH depends on the structure of the catalyst and the nature of the solvent [12] we have now tried to improve such reactions using readily available commercial additives and Cr-reagents, i.e. without sophisticated catalysts.

A variety of experimental conditions were firstly used with **1a** as the substrate; some of them are collected in Table 1. The oxidation of **1a**, carried out firstly at room temperature for 25 h in methylene chloride with CrO_3 as the catalyst and a large excess of *t*-BuOOH (7 eq.), led to 48% of **2a** and 4% of a mixture of α-and β-epoxides **3a** (run 1). Since the use of benzotrifluoride as solvent can increase the efficiency of Cr-catalyzed oxidations [23,24] and also the stability of *tert*-butylperoxychromium complexes [25] the experiment was repeated in this solvent, however, without improvement (run 2). Decreasing the amount

* Corresponding authors.
E-mail addresses: snikolar@upatras.gr (S.S. Nikolaropoulos), jacques.muzart@univ-reims.fr (J. Muzart).

1381-1169/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcata.2006.01.031

Table 1
Oxidation of cholesteryl acetate[a]

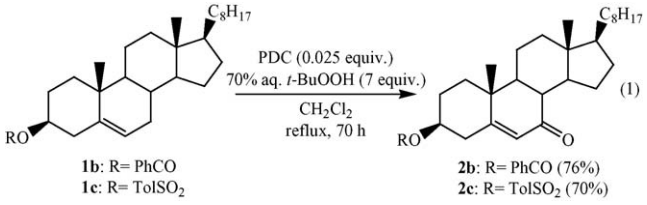


Run	Cr catalyst (eq.)	Additive (eq.)	*t*-BuOOH (eq.)	Solvent	*T* (°C)	Time (h)	Conv. (%)	Yield (%)[b]	
								2a	**3a**
1	CrO_3 (0.05)	No	7	CH_2Cl_2	rt	25	83	48	4
2	CrO_3 (0.05)	No	7	$PhCF_3$	rt	25	81	50	4
3	CrO_3 (0.05)	No	4	$PhCF_3$	rt	70	82	56	18
4	CrO_3 (0.05)	No	4	$PhCH_3$	rt	70	40	18	17
5	CrO_3 (0.05)	Py[c] (0.1)	7	CH_2Cl_2	rt	31	93	74	3
6	CrO_3 (0.05)	Py[c] (0.1)	7	$PhCF_3$	rt	31	95	76	3
7	PDC (0.1)	No	7	CH_2Cl_2	rt	24	95	74	Traces
8	PDC (0.1)	No	7	$PhCF_3$	rt	24	96	72	Traces
9	PDC (0.1)	No	7	PhCl	rt	24	96	67	4
10	PDC (0.1)	No	7	PhH	rt	64	98	59	7
11	PDC (0.1)	No	4	$PhCF_3$	rt	72	91	76	7
12	PDC (0.1)	No	4	$PhCH_3$	rt	72	31	20	7
13	CrO_3 (0.05)	No	7	$PhCF_3$	40	24	95	51	3
14	CrO_3 (0.05)	Py[c] (0.1)	7	$PhCF_3$	40	24	100	72	5
15	CrO_3 (0.05)	NMI[d] (0.1)	7	$PhCF_3$	40	23	100	74	4
16	PDC (0.025)	No	7	CH_2Cl_2	40	50	100	78	Traces
17	PCC (0.05)	No	7	CH_2Cl_2	40	66	60	41	Traces

[a] 1 mmol of substrate, 10 ml of solvent.
[b] Isolated yields.
[c] Py: pyridine.
[d] NMI: *N*-methylimidazole.

of *t*-BuOOH to 4 eq. required a longer reaction time, leading to a similar yield of **2a** but with an increasing amount of **3a** (run 3). With toluene as solvent, the conversion of **1a** dropped considerably (run 4). With pyridine as additive, the yield of **2a** increased strongly in both CH_2Cl_2 and $PhCF_3$ (runs 5 and 6). This observation urged us to test PDC as the catalyst. As expected, conversions and yields were in the same order than with the CrO_3/pyridine mixture (runs 7 and 8) [26]. Under these conditions, toluene and in particular benzene were less suitable solvents (runs 9 and 10). The use of 4 eq. of *t*-BuOOH in $PhCF_3$ for 72 h led to 91% conversion and 76% of **2a** (run 11), whereas only 31% conversion was attained in $PhCH_3$ (run 12). Further experiments were carried at 40 °C with 7 eq. of *t*-BuOOH. Again, the addition of pyridine or *N*-methylimidazole to CrO_3 led to a selective allylic oxidation in $PhCF_3$ (compare runs 14 and 15 to run 13). Interestingly, **2a** was isolated with 78% yield using only 0.025 eq. of PDC in CH_2Cl_2 (run 16), this yield being higher than the one obtained using 4 eq. of both PDC and *t*-BuOOH [6,27]. A low conversion was obtained using a Cr catalyst having a mildly acidic character [28] such as pyridinium chlorochromate (PCC) (run 17).

Under the experimental conditions of run 16, Table 1, replacing the acetoxy group in C-3 position of the substrate by a benzoyloxy or a tosyloxy group yielded the corresponding allylic oxidation products **2b** and **c**, respectively with a similar selectivity (Eq. (1)).

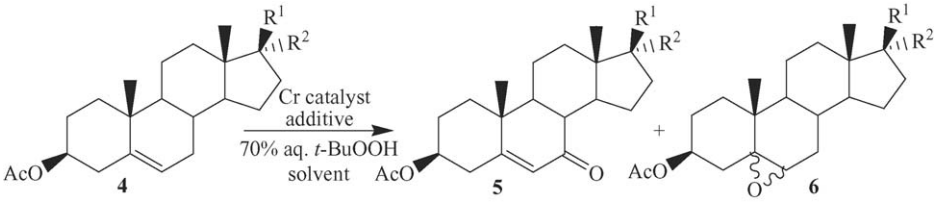


(1)

Unfortunately, the oxidation of Δ^5-steroids differently substituted in the C-17 position (**4a**–**c**) under the same conditions afforded low yields of the corresponding 5-en-7-ones (Table 2, runs 1, 8, 15). Consequently, various experimental conditions were again examined, the most interesting results being reported in Table 2. As exemplified by these selected results, optimum yields in the 7-keto-Δ^5-steroids required fitting experimental conditions for each substrate. That has also been observed for the oxidation of 3β-acetoxy-17α-aza-D-homo-androst-5-en-17-one (Table 3).

From the above results, it appears that suitable Cr-catalyzed conditions have been disclosed for the effective and selective oxidation of various Δ^5-steroids into the corresponding 7-keto-Δ^5-steroids. In some cases, benzotrifluoride is the sol-

Table 2
Oxidation of 3β-acetoxy-androst-5-en-17-one, 3β-acetoxy-pregn-5-en-20-one and 3β-acetoxy-17β-acetamido-androst-5-ene[a]



Run	Cr catalyst (eq.)	Additive (eq.)	*t*-BuOOH (eq.)	Solvent	*T* (°C)	Time (h)	Conv. (%)	Yield (%)[b]	
4a: C(R1)(R2) = C=O								**5a**	**6a**
1	PDC (0.025)	No	7	CH_2Cl_2	40	50	63	35	4
2	CrO_3 (0.05)	No	7	CH_2Cl_2	rt	25	85	78	Traces
3	CrO_3 (0.05)	Py[c] (0.1)	7	CH_2Cl_2	rt	31	91	78	Traces
4	CrO_3 (0.05)	Py[c] (0.1)	7	$PhCF_3$	rt	31	94	83	Traces
5	PDC (0.1)	No	4	$PhCF_3$	rt	72	95	82	Traces
6	CrO_3 (0.05)	NMI[d] (0.1)	7	$PhCF_3$	40	23	100	83	Traces
7	PDC (0.1)	No	7	CH_2Cl_2	rt	24	80	60	6
4b: C(R1)(R2) = C(COMe)(H)								**5b**	**6b**
8	PDC (0.025)	No	7	CH_2Cl_2	40	50	61	29	10
9	CrO_3 (0.05)	No	7	CH_2Cl_2	rt	25	98	86	Traces
10	CrO_3 (0.05)	Py[c] (0.1)	7	CH_2Cl_2	rt	31	93	80	Traces
11	CrO_3 (0.05)	Py[c] (0.1)	7	$PhCF_3$	rt	31	92	78	Traces
12	PDC (0.1)	No	4	$PhCF_3$	rt	72	94	80	2
13	CrO_3 (0.05)	NMI[d] (0.1)	7	$PhCF_3$	40	23	100	81	Traces
14	PDC (0.1)	No	7	CH_2Cl_2	rt	24	89	71	2
4c: C(R1)(R2) = C(NHAc)(H)								**5c**	**6c**
15	PDC (0.0.25)	No	7	CH_2Cl_2	40	50	58	38	Traces
16	CrO_3 (0.05)	No	7	CH_2Cl_2	rt	25	67	50	Traces
17	CrO_3 (0.05)	Py[c] (0.1)	7	CH_2Cl_2	rt	31	97	71	8
18	CrO_3 (0.05)	Py[c] (0.1)	7	$PhCF_3$	rt	31	98	89	5
19	PDC (0.1)	No	4	$PhCF_3$	rt	72	91	80	8
20	CrO_3 (0.05)	NMI[d] (0.1)	7	$PhCF_3$	40	23	100	84	4
21	PDC (0.1)	No	7	CH_2Cl_2	rt	24	85	70	Traces

[a] 1 mmol of substrate, 10 ml of solvent.
[b] Isolated yields.
[c] Py: pyridine.
[d] NMI: *N*-methylimidazole.

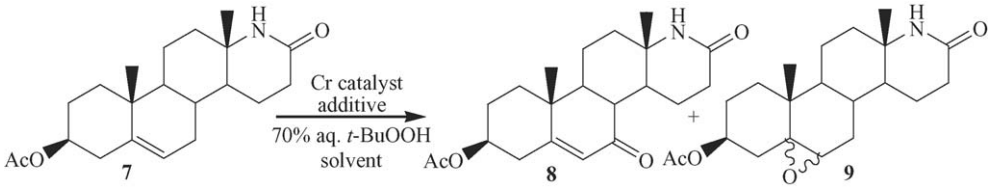
vent allowing to reach the best yields. Unfortunately, benzotrifluoride is an expensive solvent. Nevertheless, it is easily recoverable by distillation, especially when the substrate and the corresponding oxidized compounds are not volatile as already reported for the Cr-catalyzed oxidations of alcohols and benzylic methylene groups by sodium percarbonate in $PhCF_3$ [23].

General procedure

In a round bottom flask containing the catalyst (0.025–0.1 mmol) and the solvent (10 mL) were added 70% aqueous *t*-BuOOH (4–7 mmol) and, after stirring for 1–2 min, the substrate (1 mmol). After stirring under reaction temperature and time conditions indicated in Tables, the mixture was filtered over a small pad of Celite. The solvent was evaporated under reduced pressure and the residue was subjected to flash-chromatography. Elution using EtOAc/petroleum ether mixtures led to the separation of the products.

The different 7-keto-Δ^5-steroids have been identified by comparison of their spectroscopic data with those of the literature [18]. The epoxides have been identified from their ^{1}H NMR spectra, the signal at around 3 ppm being characteristic of the hydrogen in the C-6 position [15,19].

Table 3
Oxidation of 3β-acetoxy-17α-aza-D-homo-androst-5-en-17-one[a]



Run	Cr catalyst (eq.)	Additive (eq.)	*t*-BuOOH (eq.)	Solvent	*T* (°C)	Time (h)	Conv. (%)	Yield (%)[b]	
								8	**9**
1	CrO_3 (0.05)	No	7	CH_2Cl_2	rt	25	78	34	5
2	CrO_3 (0.05)	Py[c] (0.1)	7	CH_2Cl_2	rt	31	81	65	Traces
3	CrO_3 (0.05)	Py[c] (0.1)	7	$PhCF_3$	rt	31	90	81	3
4	PDC (0.1)	No	4	$PhCF_3$	rt	72	91	74	5
5	CrO_3 (0.05)	NMI[d] (0.1)	7	$PhCF_3$	40	23	100	83	3
6	PDC (0.1)	No	7	CH_2Cl_2	rt	24	91	56	Traces

[a] 1 mmol of substrate, 10 ml of solvent.
[b] Isolated yields.
[c] Py: pyridine.
[d] NMI: *N*-methylimidazole.

Acknowledgments

This research was supported by CNRS and the "K. Karathedori" grant no. 3013, Research Committee of the University of Patras, Greece.

References

[1] J. Muzart, Bull. Soc., Chim. Fr. (1986) 65–77.
[2] (a) A.A. Kandutsch, H.W. Chen, H.J. Heiniger, Science 201 (1978) 498–501;
(b) M. Numazawa, A. Mutsumi, K. Hoshi, Y. Tanaka, Biochem. Biophys. Res. Commun. 186 (1992) 32–39.
[3] H. Nagano, J.P. Poyser, K.P. Cheng, L. Bang, G. Ourisson, J. Chem. Res. (S) (1977) 218.
[4] (a) G. Lizard, S. Lemaire, S. Monier, S. Gueldry, D. Neel, P. Gambert, FEBS Lett. 419 (1997) 276–280;
(b) M. Numazawa, A. Mutsumi, M. Tachibana, K. Hoshi, J. Med. Chem. 37 (1994) 2198–2205.
[5] (a) G.W. Salmond, M.A. Barta, J.L. Havens, J. Org. Chem. 43 (1978) 2057–2059;
(b) E.J. Parish, S. Chitrakorn, Synth. Commun. 15 (1985) 393–399;
(c) E.J. Parish, S. Chitrakorn, K.L. Todd, Org. Prep. Proc. Int. 17 (1985) 192–194;
(d) E.J. Parish, T.-Y. Wei, Synth. Commun. 17 (1987) 1227–1233;
(e) E.J. Parish, H. Sun, S.A. Kizito, J. Chem. Res. (S) (1996) 544–545;
(f) A. Amann, G. Ourisson, B. Luu, Synthesis (1987) 1002;
(g) F.A. Luzzio, F.S. Guziec, Org. Prep. Proc. Int. 20 (1988) 533–584.
[6] N. Chidambaram, S. Chandrasekaran, J. Org. Chem. 52 (1987) 5048–5051.
[7] E.J. Corey, G. Schmidt, Tetrahedron Lett. (1979) 399–402.
[8] Over-stoichiometric amounts of PDC have been however used for the allylic oxidation of other Δ^5-steroids;
(a) see ref. 5d;
(b) P.M.F.M. Bastiaansen, L. Kohout, M.A. Posthupus, J.B.P.A. Wijnberg, A.J. de Grost, Org. Chem. 61 (1996) 859–867;
(c) M. Hector, R.W. Hartmann, V.C.O. Njar, Synth. Commun. 26 (1996) 1075–1082.
[9] J.A.R. Salvador, J.H. Clark, Green Chem. 4 (2002) 352–356.
[10] J. Muzart, Chem. Rev. 92 (1992) 113–140.
[11] (a) A.J. Pearson, Y.-S. Chen, S.-Y. Hsu, T. Ray, Tetrahedron Lett. 25 (1984) 1235–1238;
(b) A.J. Pearson, Y.-S. Chen, G.R. Han, S.-Y. Hsu, T. Ray, J. Chem. Soc. Perkin Trans. I (1985) 267–273.
[12] (a) J. Muzart, Tetrahedron Lett. 28 (1987) 4665–4668;
(b) J. Muzart, New J. Chem. 13 (1989) 9–11;
(c) J. Muzart, Synth. Commun. 19 (1989) 2061–2067.
[13] L.H.B. Baptistella, I.M.O. Sousa, Y. Gushikem, A.M. Aleixo, Tetrahedron Lett. 40 (1999) 2695–2698.
[14] R. Prousa, B. Schönecker, J. Prakt. Chem. 333 (1991) 775–777.
[15] M. Kimura, T. Muto, Chem. Pharm. Bull. 27 (1979) 109–112.
[16] (a) J.A.R. Salvador, J.H. Clark, Chem. Commun. (2001) 33–34;
(b) J.H. Clark, J.A.R. Salvador, WO 2002016391, 2002; Chem. Abstr (2002) 157798;
(c) M. Jurado-Gonzalez, A.C. Sulliwan, J.R.H. Wilson, Tetrahedron Lett. 44 (2003) 4283–4286.
[17] (a) J.A.R. Salvador, M.L. Sá e Melo, A.S. Campos Neves, Tetrahedron Lett. 38 (1997) 119–122;
(b) J.A.R. Salvador, M.L. Sá e Melo, A.S. Campos Neves, US 97-901764 (1997); Chem. Abstr. (2001) 464392.
[18] E.S. Arsenou, A.I. Koutsourea, M.A. Fousteris, S.S. Nikolaropoulos, Steroids 68 (2003) 407–414.
[19] M. Kimura, T. Muto, Chem. Pharm. Bull. 28 (1980) 1836–1841.
[20] (a) R.A. Miller, A.S. Thompson, R.K. Bakski, E.G. Corley, WO 9532215 (1995); Chem. Abstr. (1996) 115197;
(b) R.A. Miller, W. Li, G.R. Humphrey, Tetrahedron Lett. 37 (1996) 3429–3432;
(c) M. Harre, R. Haufe, K. Nickisch, P. Weinig, H. Weinmann, Org. Process Res. Dev. 2 (1998) 100–104;
(d) M.E. Jung, T.W. Johnson, Org. Lett. 1 (1999) 1671–1674.
[21] J.A.R. Salvador, S.M. Silvestre, Tetrahedron Lett. 46 (2005) 2581–2584.
[22] (a) M. Di Filippo, I. Izzo, L. Savignano, P. Tecilla, F. De Riccardis, Tetrahedron 59 (2003) 1711–1717;
(b) Y. Zheng, Y. Li, J. Org. Chem. 68 (2003) 1603–1606;
(c) V. Pouzar, I. Černy, M. Hill, M. Bičiková, R. Hampl, Steroids 70 (2005) 739–749;
(d) Z. Hua, D.A. Carcache, Y. Tian, Y.-M. Li, S.J. Danishefsky, J. Org. Chem. 70 (2005) 9849–9856.
[23] N. Delaval, S. Bouquillon, F. Hénin, J. Muzart, J. Chem. Res. (S) (1999) 286–287.
[24] S. Boitsov, A. Riahi, J. Muzart, C. R. Acad. Sci. Paris, Série IIc 3 (2000) 747–750.

[25] S. Boitsov, J. Songstad, J. Muzart, J. Chem. Soc., Perkin Trans. II (2001) 2318–2323.
[26] For the PDC-catalyzed allylic oxidation of a non-steroidal substrate with *t*-BuOOH, see: A.G. Schultz, T.J. Guzi, E. Larsson, R. Rahm, K. Thakkar, J.M. Bidlack, J. Org. Chem. 63 (1998) 7795–7804.
[27] The high efficiency of low amounts of PDC to catalyze the benzylic oxidation of indane with *t*-BuOOH in CH_2Cl_2 has been already observed: J. Muzart, A. N'Aït Ajjou, J. Mol. Catal. 66 (1991) 155–161.
[28] E.J. Corey, J.W. Suggs, Tetrahedron Lett. (1975) 2647–2650.