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Copper-Catalysed Allylic Oxidation of Δ^5-Steroids by *t*-Butyl Hydroperoxide

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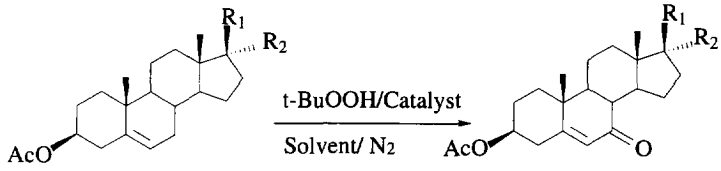
Abstract: Δ^5-7-Oxosteroids are efficiently prepared from Δ^5-steroids with *t*-BuOOH and a copper catalyst, either Cu(II) and Cu (I) salts or Cu metal; selectivity in the presence of a secondary alcohol is observed.

Allylic oxidation belongs to an important group of olefin oxidations and remains a reaction of considerable value in organic synthesis[1,2]. Δ^5-Steroids can lead through oxidation to 5-en-7-ones, known to be inhibitors of sterol biosynthesis and with some use in cancer chemotherapy, since they are more toxic towards tumorous than non tumorous cells[3].

These allylic oxidation reactions have been traditionally performed with chromium reagents, as CrO_3-pyridine complex[4], chromium trioxide and 3,5-dimethylpyrazole[5], pyridinium chlorochromate (PCC)[6,7], pyridinium dichromate (PDC)[7], sodium chromate[8], and sodium dichromate in acetic acid[9]. However the great excess of reagent and the large volume of solvent used in these procedures, along with a difficult work-up of the environmentally hazardous chromium residues, becomes very inconvenient for large scale reactions.

Of greater preparative interest is the use of hydroperoxides with different types of catalysts[10-16] to perform these reactions.The use of CrO_3 as catalyst[10] gives the allylic oxidation products, Δ^5-7-ketones, but the epoxidation of the double bond is also observed, although remained a *minor* reaction pathway.In spite of the good yields reported with hexacarbonyl chromium, $Cr(CO)_6$[11,12], pyridinium dichromate[13] and $RuCl_3$[14] to prepare allylic oxidation products from Δ^5-steroids, the toxicity of the chromium reagents and the high cost of the ruthenium catalyst encouraged us to find new methods for this reaction.

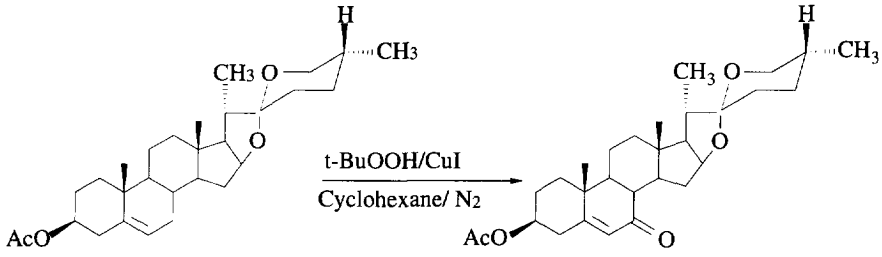
In this communication we report the use of cuprous and cupric salts, besides copper metal as catalysts, for this type of reactions.Using Δ^5-3β-acetoxy steroids **1,3**, **5** and **7** as substrates (Scheme 1), allylic oxidation products **2,4** , **6** and **8**[17] were obtained in very high yield, 75% to 84% (Table 1). The presence of catalyst is essential, since no reaction is detected in the absence of copper species.Apart the reaction whith substrate **1** and **7**, which required apolar solvents as benzene and cyclohexane and a temperature of 65-70°C, all the reactions were performed in acetonitrile using a milder temperature, 50-55°C. The best result was obtained with copper powder (Aldrich, 150 mesh) as catalyst, which is transformed *in situ* into a soluble copper compound. Similar observation was reported recently for the copper catalysed oxidation of hydroxy compounds by *t*-butyl hydroperoxide under phase transfer conditions[18].



1 $R_1=C_8H_{17};R_2=H$ **2**

3 $R_1;R_2=O$ **4**

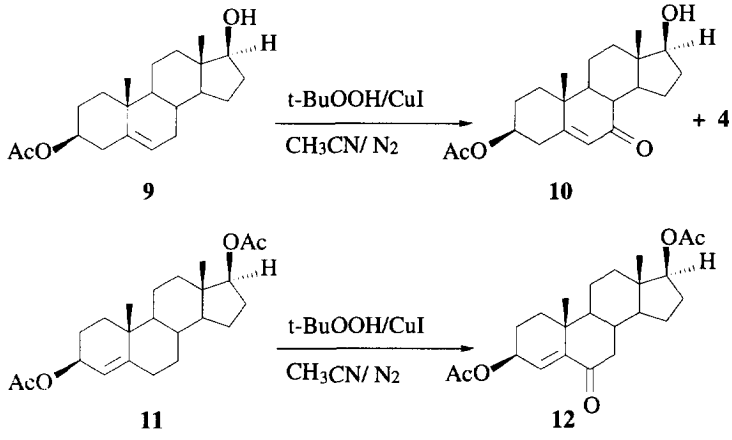
5 $R_1=COCH_3;R_2=H$ **6**



7 **8**

Scheme 1

Typical procedure: to a solution of 17-oxoandrost-5-en-3β-yl acetate, **3** (330.45mg/1mmole) in acetonitrile (6ml) under nitrogen, copper iodide (2mg/0.010 mmoles) and t-butyl hydroperoxide (1.2ml / 6-7mmoles) were added.After 20 hours, under magnetic stirring at 50°C, the solution was poured into sodium sulphite solution (10% aq.) and extracted with diethyl ether. The extract was washed with aq.saturated solution of $NaHCO_3$, brine and water, dried ($MgSO_4$) and evaporated to dryness to give the 7,17-dioxoandrost-5-en-3β-yl acetate **4**.



9 **10**

11 **12**

Scheme 2

The reactions performed on the Δ^5-3β-acetoxy substrates **1,3,5** and **7** were very selective when compared

Table1. Allylic oxidation of Δ^5-Steroids

Substrate 1mmole	*t*-BuOOH[a] (ml)	Catalyst (mmoles)		Solvent	Time (h)	Temp. (°C)	Prod.	Yield (%)
1	1.2	CuI	(0.026)	Benzene	24	70	**2**	80[b]
3	1.2	CuI	(0.010)	CH_3CN	20	50	**4**	83
3	1.2	CuBr	(0.02)	"	24	55	**4**	80[c]
3	1.2	CuCl	(0.015)	"	18	55	**4**	81[c]
3	1.2	$CuCl_2$	(0.02)	"	24	55	**4**	81[c]
3	1.0	Cu	(0.03)	"	16	50	**4**	84
5	1.2	CuI	(0.007)	"	20	55	**6**	80[c]
7	2.0	CuI	(0.042)	Cyclohexane	72	65	**8**	75[d]
9	1.0	CuI	(0.015)	CH_3CN	24	50	**10**	70[e]

[a] 5.0-6.0M solution in decane(Aldrich).

[b] 14% of starting material was recovered by flash chromatography (10% ethyl acetate in petroleum ether 40-60° C).

[c] Traces of starting material and a by-product are visible on t.l.c. plates but not detectable in ^{1}H-NMR spectrum (500MHz) of the crude product.

[d] The crude product contains 10% of starting material, calculated on the basis of the ^{1}H-NMR signal (6-H).

[e] Calculated on the basis of the ^{1}H-NMR signal (6-H) of the crude product (**10+4**).

with the use of *t*-BuOOH and $Fe(acac)_3$ as catalyst, by Kimura *et al.* [15,16], where the 7-ketone comes along with epimeric 7-alcohols and 7-alkylperoxides. Replacement of $Fe(acac)_3$ by $Mo(CO)_6$ has been also described but leading to epoxidation of cholesteryl acetate with alkyl hydroperoxides in benzene[16]. The same outcome is seen when $Fe(acac)_3$ catalyses the oxidative reactions with H_2O_2. 5,6-Epimeric epoxides were the *major* products.

In previous papers Pearson *et al.* reported that allylic oxidation proceeds selectively in the presence of some secondary alcohols using $Cr(CO)_6$ as catalyst. Attempts to study this selectivity, led us to use substrate **9** with CuI as catalyst (Scheme 2). Compound **10**[17] was the *major* product (70%) corroborating the previous findings.In contrast to these results, the Δ^4-3β-acetoxyandrostane **11** showed a very low reactivity under the same conditions, leading to 4-en-6-one **12** in very low yield.The metal catalyzed decomposition of peroxide reagents is well documented[19], and our results probably agree with the formation of alkyl hydroperoxides as intermediates, which fragment subsequently to furnish ketones or alcohols as reported by Barton *et al.*[20]. For the Δ^5-steroids under the conditions studied, the formation of enones has been largely favoured.

In summary, we report a new and efficient method for the preparation of Δ^5-3β-acetoxy-7-oxo steroids from a variety of easily available Δ^5-3β-acetoxy substrates with *t*-BuOOH catalysed by copper (I), (II) or copper metal. The use of these species can be indiscriminated but is absolutely necessary with the advantage of being inexpensive and less toxic than Cr reagents.A study on the effect of oxygen and of other types of catalysts on this reaction is under investigation.

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REFERENCES AND NOTES:

1. Muzart, J. *Bull.Soc.Chim. Fr.*,**1986**,65.
2. Bulman Page, P.C. and McCarthy ,T.J., in *Comprehensive Organic Synthesis* ed. B. M. Trost, I.Fleming, Pergamon Presss, Oxford, NewYorK, Seoul,Tokyo, **1991**, vol.7,p. 83.
3. Sato,Y.; Sonoda,Y.; Morisaki,M.; Ikekawa,N. *Chem. Pharm. Bull*,**1984**, 32, 3305; Chen,K.P.; Nagana,H.; Bang, L.; Ourisson, G.*J. Chem. Res.* (S), **1977**, 217; Nagana, H.; Poyser,J.P.; Cheng,K.P.; Bang, L.; Ourisson ,G. *J. Chem. Res.* (S), **1977**, 218; Kumar,V.; Alain,A.; Ourisson,G.; Luu.,B.*Synt. Commun.*, **1987**, 17, 1279.
4. Dauben,G.W.; Lorber, M.; Fullerton,D.S. *J.Org. Chem*, **1969**, 34, 3587; Fullerton,D.S.; Chen,C.M. *Synt. Commun.*, **1976**, 6, 217.
5. Salmond,W.G.; Barta,M.A.; Havens,J.L. *J.Org. Chem.*, **1978**, 43, 2057.
6. Parish,E.J. ; Chitrakorn ,S.; Wei,T.-Y. *Synt. Commun.*,**1986**, 16, 1371.
7. Parish,E.J. and Wei,T.-Y. *Synt.Commun.*, **1987**,17, 1227.
8. Marshall,C.W.; Ray,R.E.; Laos,I. and Riegel,B. *J. Am.Chem. Soc.*, **1957**, 79, 6308.
9. Amann, A.; Ourisson,G.; Luu , B. *Synthesis*, **1987**, 1002.
10. Muzart, J. *Tetrahedron Lett.*, **1987**, 28, 4665.
11. Pearson, A.J.; Chen,Y.S.; Hsu, S.Y.; Ray ,T.*Tetrahedron Lett.*, **1984**, 25, 1235.
12. Pearson, A.J.; Chen,Y.S.; Hang,G.R.; Hsu, S.Y. ; Ray ,T. *J. Chem Soc.Perkin Trans.*1, **1985**, 267.
13. Chidambaram, N.; Chandrasekaran, S. *J.Org.Chem*, **1987**, 52, 5048.
14. Miller, R.A.; Li,W. and Humphrey, G.R.*Tetrahedron Lett.*, **1996**, 37, 3429.
15. Kimura, M.; Muto,T. *Chem. Pharm. Bull.*, **1979**, 27, 109.
16. Kimura, M.; Muto,T. *Chem. Pharm. Bull.*, **1980**, 28, 1836.
17. **2**:^{1}H NMR ($CDCl_3$,500MHz) δ 0.68 (s,18-H3),1.21 (s, 19-H3), 0.92 (d, J=6Hz, 21-H3), 0.86 (d, J=6Hz , 26-H3, 27-H3), 2.05 (s, CH_3CO), 4.69 (m, 3α-H), 5.70 (m, 6-H),^{13}C NMR ($CDCl_3$,75MHz) (C_3)72.17, (C_6)126.64, (C_5)163.82, ($CH_3\underline{C}O$)170.22, (C_7) 201.87 ;**4:**^{1}H NMR ($CDCl_3$,500MHz) δ 0.9 (s,18-H3), 1.24 (s, 19-H3), 2.05 (s,CH_3CO),4.72 (m, 3α-H), 5.76(m, 6-H), ^{13}C NMR ($CDCl_3$,75MHz) (C_6) 126.64 , (C_5)163.82, ($CH_3\underline{C}O$)170.19, (C_7) 200.66 , (C_{17}) 220.14; **6:**^{1}H NMR ($CDCl_3$,500MHz) δ 0.66 (s, 18-H3), 1.22 (s, 19-H3) , 2.13 (s, 21-H3), 2.05 (s,CH_3CO), 4.71 (m, 3α-H), 5.72 (m, 6-H),^{13}C NMR($CDCl_3$,75MHz) (C_3) 72.04, (C_6)126.43, (C_5)164.15 , ($CH_3\underline{C}O$)170.27, (C_7) 201.13 , (C_{20}) 209.67;**8:**^{1}H NMR ($CDCl_3$,500MHz) δ 0.79 (s, 18-H3), 1.23 (s, 19-H3) 2.06 (s,CH_3CO), 4.69 (m, 3α-H), 5.71 (m, 6-H)^{13}C NMR($CDCl_3$,75MHz) (C_3) 72.14, (C_{16})80.94, (C_{22})109.22, (C_6)126.51, (C_5)164.09 , ($CH_3\underline{C}O$)170.32, (C_7) 201.43 ;**10:**^{1}H NMR ($CDCl_3$,500MHz) δ 0.78 (s, 18-H3), 1.24 (s, 19-H3), 2.06 (s,CH_3CO),4.72 (m,3α-H), 3.66 (m,17α-H), 5.71 (m, 6-H),^{13}C NMR ($CDCl_3$,75MHz) (C_3)72.04, (C_6)126.43, (C_5)164.31,($CH_3\underline{C}O$)170.24, (C_7) 201.53.
18. Feldberg, L.; Sasson,Y.; *J. Chem. Soc.Chem.Commun.***1994**, 1807.
19. Sheldon, R.A.; Kochi, J.K. *Adv.Catal.*,**1976**, 25, 272.
20. Barton, D.H.R.; Bévière,S.D.; Chavasiri,W.; Doller, D. and Hu, B. *Tetrahedron Lett.*, **1993**, 34, 567, and references cited therein.

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