

Bismuth-catalyzed allylic oxidation using *t*-butyl hydroperoxide

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Abstract—Bismuth(III) salts are efficient catalysts for the selective allylic oxidation using *tert*-butyl hydroperoxide. BiCl_3 is especially effective and can be easily recovered and reused as BiOCl . Using $\text{BiCl}_3/\text{K-10}$ as catalyst, an increase in the reaction rate was observed.

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Allylic oxidation is an organic reaction of significant interest to organic chemists with applications in areas ranging from agricultural products to pharmaceuticals.^{1,2}

The allylic oxidation of steroids is a particularly important subject and has attracted interest over many years. An example of the former is the oxidation of Δ^5 -steroids to their corresponding 5-en-7-ones, which are known inhibitors of sterol biosynthesis and have a large use in therapy.³

A variety of chromium reagents⁴ have been used for the allylic oxidation of unsaturated steroids. Examples include CrO_3 -pyridine complex, CrO_3 and 3,5-dimethylpyrazole, pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), sodium chromate, sodium dichromate in acetic acid, pyridinium fluorochromate and 3,5-dimethylpyrazolium fluorochromate (VI). However, the large quantities of ecologically and physiologically undesirable chromium reagents and the large volume of solvent required in these procedures, in combination with the difficult work-up causes such procedures to be inconvenient on a commercial scale.

Of greater preparative interest has been the use of hydroperoxides combined with different types of metal catalysts^{5–10} to prepare allylic oxidation products from Δ^5 -steroids. Despite the good yields reported with

CrO_3 ,⁵ hexacarbonylchromium $\text{Cr}(\text{CO})_6$,⁶ pyridinium dichromate⁷ and RuCl_3 ,⁸ the toxicity of these chromium compounds and the high cost of the ruthenium catalyst led us to search for more environmentally acceptable methods based on the use of copper⁹ and cobalt¹⁰ catalysts. However, a difficult separation step is needed to remove such catalysts, which cannot easily be recovered and reused.

The heterogenization of inorganic reagents and catalysts useful in organic reactions is a very important area in clean technology.¹¹ We have recently reported the use of cobalt, copper, manganese and vanadium catalysts in heterogeneous forms¹² for this type of allylic oxidation reaction. Jurado-Gonzalez et al.¹³ reported similar results using *tert*-butyl hydroperoxide and catalytic amounts of cobalt (II) alkyl phosphonate modified silica. Recently, Marwah et al. reported¹⁴ an economical and green approach for the oxidation of olefins to enones, using household laundry bleach and aqueous *tert*-butyl hydroperoxide, but with lower isolated technical product yields.

Compared with the copper⁹ and cobalt¹⁰ catalysts reported in previous papers, in spite of its heavy metal status, bismuth is considered safe, as it is non-toxic and non-carcinogenic.

Bismuth has been used in medicinal preparations and some bismuth compounds such as bismuth subnitrate and bismuth subcitrate have been used as treatment for gastric disorders.¹⁵ The increasing concern about environment and the need for 'green reagents' has focused bismuth and its compounds over the last decade.¹⁶

Keywords: Allylic oxidation; Unsaturated compounds; Bismuth; *t*-Butyl hydroperoxide.

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In this communication¹⁷ we report the use of bismuth salts in homogeneous and heterogeneous forms ($\text{BiCl}_3/\text{K-10}$ montmorillonite), for this type of allylic oxidation reaction. Using Δ^5 -steroids **1–5** and valencene **6** as substrates (Scheme 1), allylic oxidation products **7–11** and **12** were obtained in very high isolated yields (Tables 1 and 2). In general, the reactions required acetonitrile as solvent and a temperature of 70 °C. The best results were obtained using BiCl_3 as catalyst in homogeneous (BiCl_3 , Table 1, entry 1) and heterogeneous forms ($\text{BiCl}_3/\text{K-10}$, Table 2, entry 10).

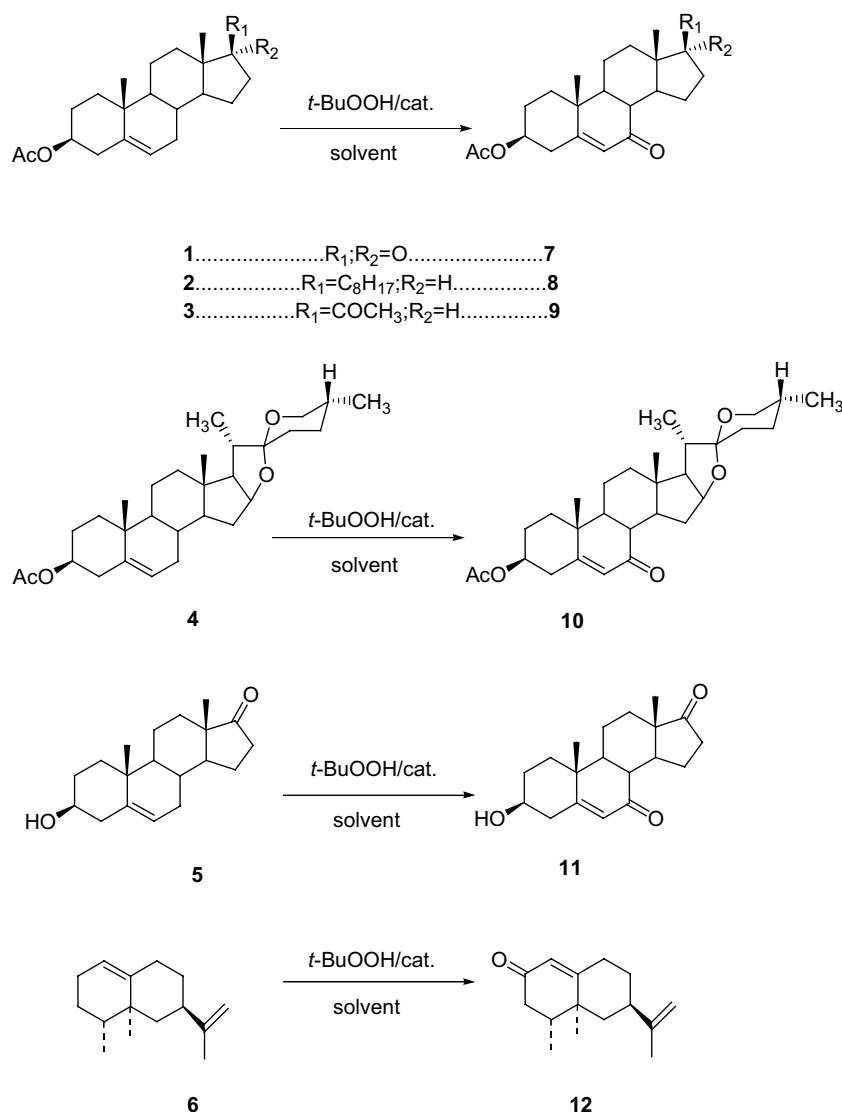
No significant reaction occurs in the absence of catalyst or in the presence of the catalyst's support only. The use of *t*-BuOOH 70% aq led to a decrease in both yields and reaction rate (Table 1, entries 7 and 8).

These reactions are very selective compared to those reported by Kimura and Muto¹⁸ carried out using $\text{Fe}(\text{acac})_3$ as catalyst. $\text{Mo}(\text{CO})_6$ led to the epoxidation of cholesteryl acetate under similar oxidative conditions as also reported by Kimura and Muto.¹⁹

In previous papers, Pearson et al. reported⁶ that allylic oxidation proceeds selectively in the presence of some secondary alcohols using $\text{Cr}(\text{CO})_6$ as catalyst. Similar chemoselectivity was reported using copper⁹ and other metal catalysts.¹⁰ Attempts to study this selectivity using substrate **5** and BiCl_3 as catalyst led to a significant increase in chemoselectivity. Compound **11** was the only product of the reaction detectable on ^1H NMR spectrum of the crude product although small traces of a by-product were visible on TLC plates (Table 2, entry 6).

Thus, a similar oxidation can be performed on valencene **6**. Using BiCl_3 as catalyst, the sesquiterpenoid nookatone **12** was the major product obtained (35% yield, Table 2, entry 7). In agreement with these results, when performed on a larger scale only a small decrease in the reaction rate was observed.

It is interesting to note that although the BiCl_3 under these reaction conditions provided a homogeneous solution, after complete reaction time a white powder was



Scheme 1.

Table 1. Allylic oxidation of dehydroepiandrosterone acetate **1** catalyzed by bismuth(III) compounds^a

Entry	Substrate/mmol	<i>t</i> -BuOOH ^b (mL)	Catalyst/mmol	Time (h)	Prod.	Isolated yield ^d (%)
1	1/0.5	0.9	BiCl ₃ /0.05	20	7 ^c	88
2	1/0.5	0.9	Bi(NO ₃) ₃ ·5H ₂ O/0.05	36	7	84
3	1/0.5	0.9	Bi ₂ O ₃ /0.05	78	7	79
4	1/0.5	0.9	Bi(CH ₃ COO) ₃ /0.05	102	7	87
5	1/0.5	0.9	BiOCl/0.05	102	7	86
6	1/0.5	0.9	Bismuth oxynitrate/0.03	113	7	80
7	1/0.5	0.7 ^c	BiCl ₃ /0.05	38	7	68
8	1/0.5	0.7 ^c	Bi(CH ₃ COO) ₃ /0.05	120	7	67

^a Reactions performed in CH₃CN, at 70 °C.^b 5.0–6.0 M solution in decane (Aldrich).^c 70% aqueous solution (Aldrich).^d Traces of starting material and a by-product are visible in TLC plates but not detectable in ¹H NMR spectrum (300 MHz).^e Crystallization from methanol afforded 77% of pure product.**Table 2.** Allylic oxidation of Δ⁵-steroids and (+)-valencene catalyzed by homogeneous and heterogeneous BiCl₃

Entry	Substrate/mmol	<i>t</i> -BuOOH ^a (mL)	Catalyst/mmol	Solvent	Time (h)	Temp. (°C)	Prod.	Isolated yield ^b (%)
1	2/0.5	0.9	BiCl ₃ /0.05	CH ₃ CN	22	70	8 ^c	82
2	3/0.5	0.9	BiCl ₃ /0.05	CH ₃ CN	22	70	9 ^d	78
3	4/0.5	0.9	BiCl ₃ /0.05	CH ₃ CN	24	70	10	60 ^e
4	4/0.5	0.9	BiCl ₃ /0.05	CH ₃ CN	44	60	10	62 ^e
5	4/0.5	0.9	BiCl ₃ /0.05	Cyclohexane	24	70	10	61 ^e
6	5/0.5	0.9	BiCl ₃ /0.05	CH ₃ CN	18	70	11	80
7	6/1.25	2.25	BiCl ₃ /0.125	CH ₃ CN	24	70	12	35 ^e
8	1/3	5.4	BiCl ₃ /0.3	CH ₃ CN	50	70	7	88
9	5/3	5.4	BiCl ₃ /0.3	CH ₃ CN	28	70	11	70
10	1/0.5	0.9	BiCl ₃ /K-10/0.05	CH ₃ CN	13	70	7	89
11	3/0.5	0.9	BiCl ₃ /K-10/0.05	CH ₃ CN	15	70	9	84
12	5/0.5	0.9	BiCl ₃ /K-10/0.05	CH ₃ CN	11	70	11	77

^a 5.0–6.0 M solution in decane (Aldrich).^b Traces of starting material and a by-product are visible in TLC plates but not detectable in ¹H NMR spectrum (300 MHz).^c Crystallization from methanol afforded 74% of pure product.^d Crystallization from methanol afforded 70% of pure product.^e Recovered by flash chromatography (ethyl acetate–light petroleum, bp 40–60 °C).

observed in suspension. The recovery of this white powder by filtration, drying and its submission to X-ray diffraction analysis, allowed us to conclude that BiCl₃ was converted to BiOCl under these reaction conditions. Tested against a pure form of BiOCl (Table 1, entry 5), the recovered catalyst in the form of BiOCl, gave identical reaction rates and isolated product yields.

The easier recovery of the catalyst in heterogeneous reactions makes them more environmentally friendly processes and led us to use BiCl₃/K-10 as catalyst²⁰ for this reaction using substrates **1**, **3** and **5**. The product yields of the allylic oxidation remained very similar but an increase in the reaction rate was observed under these conditions (Table 2, entries 10, 11 and 12).

A study of the effects of different oxidants and other types of heterogeneous bismuth catalysts on this and related reactions is presently under progress.

In summary, we have discovered an efficient method for allylic oxidation of both unsaturated steroids and valencene in very good yields and high selectivity, using *t*-BuOOH as the oxidant and homogeneous and heterogeneous Bi(III) as the catalyst.

Typical procedure: To a solution of 17-oxoandrost-5-en-3β-yl acetate **1** (165 mg, 0.5 mmol) in acetonitrile (3 mL), catalyst BiCl₃ (16 mg, 0.05 mmol) and *tert*-butyl hydroperoxide (0.9 mL, 5 mmol, 5.0–6.0 solution in decane, Aldrich) were added.

After 20 h under magnetic stirring at 70 °C, the catalyst was removed by filtration and the solution was poured into sodium sulfite solution (10% aq) and extracted with diethyl ether. The extract was washed with aq saturated solution of NaHCO₃, water, dried and evaporated to dryness to give 7,17-dioxoandrost-5-en-3β-yl acetate **7** (88% yield).

Spectroscopic data for **7**,¹² **8**,⁹ **9**,^{6b} **10**,^{6b} **11**²¹ and **12**¹² are in agreement with those reported in the literature.

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