Efficient Aerobic Oxidation of Acetals to Esters Catalyzed by *N*-Hydroxy phthalimide (NHPI) and Co(II) under Mild Conditions

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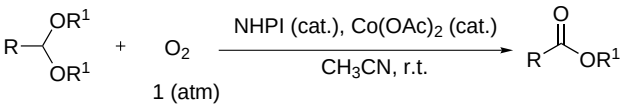
Received 24 March 2003; revised 21 July 2003

Abstract: Efficient oxidation of a variety of structurally diverse acetals, including open-chain acetals, 1,3-dioxanes, 1,3-dioxalanes, with molecular oxygen using catalytic amounts of *N*-hydroxyphthalimide (NHPI) in the presence of $Co(OAc)_2$ as co-catalyst was investigated.

Key words: esters, catalysis, oxidation

The protection of carbonyl compounds or diols as acetals is of paramount importance in organic synthesis as shown by a large number of methods that have been developed for this key transformation.[1] Moreover, direct oxidation of both acetals and also aldehydes to the corresponding esters is an interesting transformation in organic chemistry as testified by a large number of reagents applied in this reaction.[2] This transformation was traditionally carried out using stoichiometric amounts or Chromium salts,[3] peracetic acid,[4] DDQ,[5] sodium perborate,[6] halogen-based reagents,[7] Oxone,[8] $VO(OAc)_2$,[9] etc. However, almost the entirety of these protocols leads to expensive processes and the formation of toxic by-products. Several other methods, especially based on the use of inexpensive reagents such as H_2O_2, *t*-BuOOH were also developed for this purpose, i.e. H_2O_2 and HCl,[10] MTO–H_2O_2,[11] *t*-BuOOH/Pd(II),[12] O_3,[13] and V_2O_5–H_2O_2.[14] With rare exceptions, most of these protocols also suffer from drawbacks such as use of excess of reagent, drastic conditions, and tedious work-up. In many instances the methods afforded the corresponding esters in low yield. From both environmental and economical point of views, the utilization of molecular oxygen as final oxidant in oxidation processes became increasingly attractive in recent years. Unfortunately, despite the importance and attractiveness of this opinion, less attention has been paid to the development of new protocols for efficient oxidations of acetals to the corresponding esters using molecular oxygen.[15] It has been shown by the elegant works of Ishii and coworkers that the aerobic oxidation of various types of hydrocarbons using *N*-hydroxyphthalimide (NHPI) as a key radical generator can be achived.[16] Along this line, for example, oxidation of alkyl benzenes at normal pressure of O_2 and ambient temperature,[17] epoxidation of alkenes,[18] selective oxidation of sulfides to sulfoxides,[19] catalytic nitration of alkenes,[20] oxidation of alcohols,[21] and oxygenation of alkynes to α,β-acetylenic ketones[22] in the presence of NHPI as key catalyst were reported. Recently it has been shown that benzylidene acetals undergo oxidative cleavage to give hydroxy mono-benzoate esters with molecular oxygen in the presence of NHPI/MCPBA/$Co(OAc)_2$ in ethyl acetate at ambient temperature.[23] Unfortunately, the scope of this method is limited to only a few examples of benzylidene acetals. Moreover, in the course of our studies, we found that this transformation proceeded equally in both acetonitrile and ethylacetate *without the use of any added MCPBA*. Therefore, we decided to disclose our recent finding on the use of NHPI as a catalyst for the direct aerobic oxidation of a variety of structurally different acetals to the corresponding esters (Scheme 1).

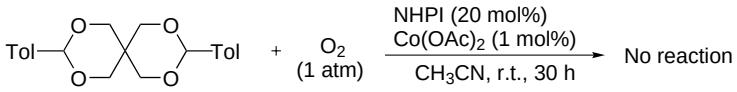


Scheme 1

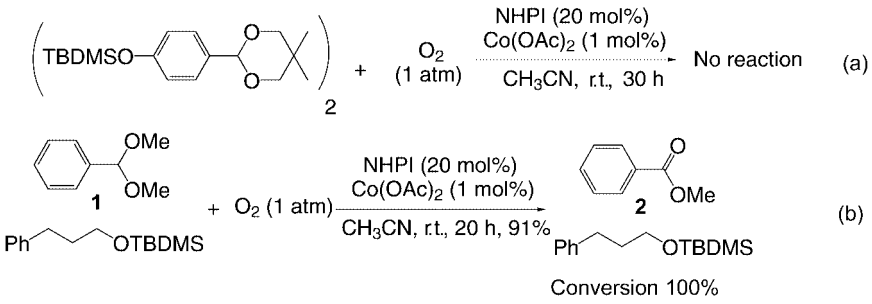
We first examined the aerobic oxidation of (dimethoxymethyl)benzene (**1**) as a model compound in the presence of a catalytic amount of NHPI in CH_3CN. The reaction of **1** in the presence of NHPI (10 mol%) under O_2 (1 atm) for 20 hours afforded a trace amount of methyl benzoate (**2**) at room temperature. When the similar reaction was carried out using the same reagents and a catalytic amount of $Co(OAc)_2$ (0.5 mol%), **2** was formed with almost 70% conversion. However, after optimization, the best ratios for substrates, reagent and also reaction conditions were found to be: **1** (1mmol), NHPI (20 mol%), $Co(OAc)_2$ (1 mol%), O_2 (1 atm) and room temperature, respectively. Thus, we observed that under the above-optimized conditions, **1** was completely converted into **2** giving 91% isolated yield (Table 1, entry 1; Scheme 3, b).

Similarly, the aerobic oxidation of various types of substituted benzaldehyde dialkylacetals using the NHPI/Co(II) system furnished the corresponding alkyl benzoates in good to excellent yields (Table 1, entries 2–6). It is noteworthy that the oxidation of cyclic acetals like 1,3-dioxolanes or 1,3-dioxanes is of some interest because it represents a route to selectively prepare the corresponding diol monoesters. We found that the oxidation of a number of aromatic 1,3-dioxolanes and 1,3-dioxanes as well as aliphatic counter parts afforded the corresponding diol

SYNTHESIS 2003, No. 15, pp 2373–2377
Advanced online publication: 29.09.2003
DOI: 10.1055/s-2003-42396; Art ID: Z04203ss.pdf



Scheme 2 Tol = *p*-MeC_6H_4-



TBDMS = tert-BuMe2Si-
Conversions were determined by NMR

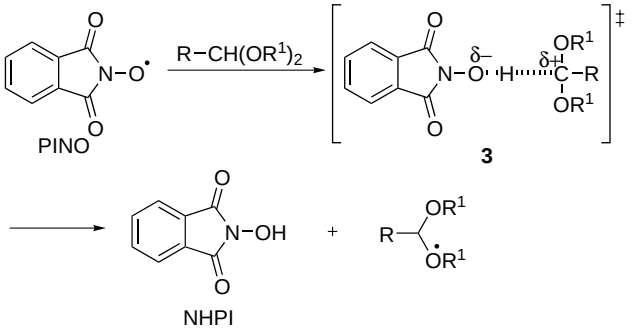
Scheme 3

monoesters in high yields (Table 1, entries 7–17). It is also worth mentioning that no oxidation of the hydroxy group on the resulting diol monoester took place at all. Surprisingly, we have observed that both pentaerythritol diacetals are thoroughly stable toward the reaction conditions even after 30 h (Scheme 2). At this time we have not any explanation for the preservation of the acetal groups in pentaerythritol diacetal systems.

Moreover, acid sensitive substrates such as aliphatic and aromatic TBDMS ethers remain intact under these conditions (Scheme 3, a).

Aromatic acetals bearing strong electron-withdrawing groups such as 4-nitrophenyl survived under the described reaction conditions (Table 1, entries 18, 19). Furthermore, application of the present protocol to the oxidation of cyclic acetals derived from α,β-unsaturated systems was not successful and a complex mixture of unidentified products was formed along with the desired diol monoesters (Table 1, entry 20).

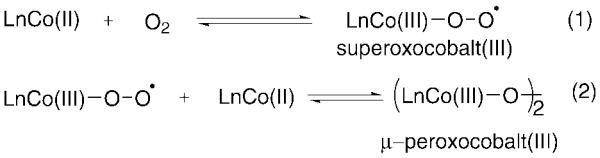
Inspection of the data in Table 1 clearly shows that the oxidation of acetals (especially aromatic acetals) is strongly governed by polar effects since electron-donating groups accelerate the rate of the oxidation reaction and electron-withdrawing groups act in the reverse manner. It has also been shown previously that in situ generated phthalimid



Scheme 4

N-oxyl radical (PINO) acts as the actual hydrogen-abstracting species from C–H bonds through a free radical chain.[16,24] Therefore, similar to Minisci's observation, we also believe that a polar transition state like **3** operates in the second state of radical chains (Scheme 4).

It is well known that the interaction of Co(II) complexes with molecular oxygen generates the corresponding labile superoxocobalt(III) or μ-peroxocobalt(III) complexes, respectively, via one-electron reduction of dioxygen



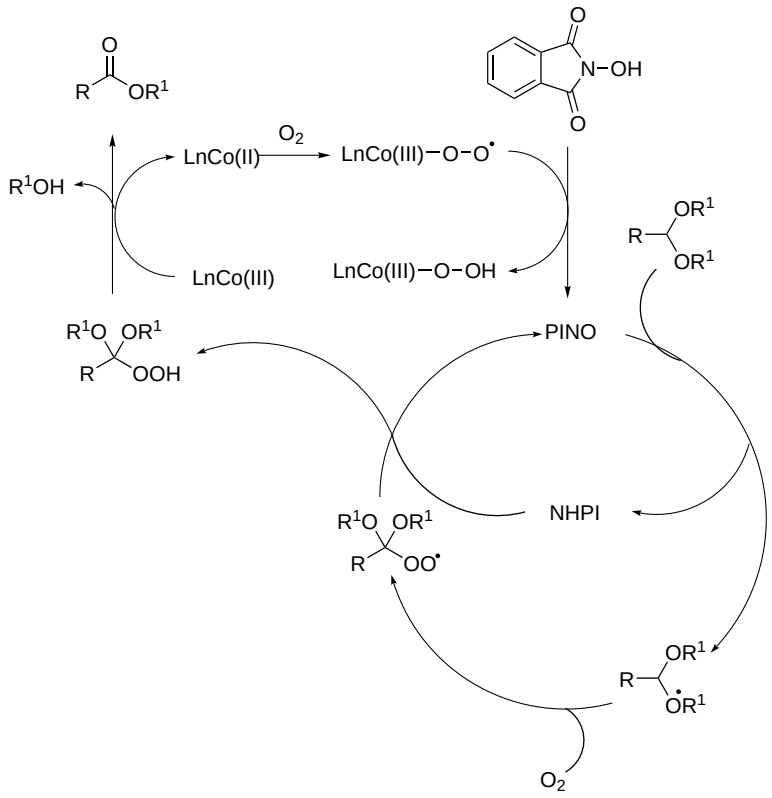
Equation 1

(Equation 1).[25]

These species presumably assist the generation of the PINO radical from NHPI at room temperature.[16] Therefore, a plausible reaction pathway for aerobic oxidation of acetals using the NHPI/Co(II) system is outlined in Scheme 5.

In conclusion, we have demonstrated that the use of NHPI combined with $Co(OAc)_2$ is a catalytic system for the efficient and environmentally benign oxidation of a series of open-chain as well as cyclic acetals with molecular oxygen.

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker 250 or 500 MHz spectrometer in $CDCl_3$ as the solvent and TMS as internal standard. All of the products are known and most of them are commercially available and were identified through comparison of their ^1H, ^{13}C, and IR spectra with those of authentic samples.



Scheme 5

Table 1 Aerobic Oxidation of Acetals to Esters Using NHPI/$Co(OAc)_2$ at Room Temperature

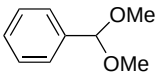
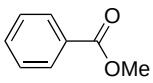
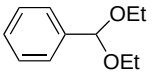
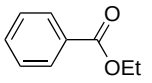
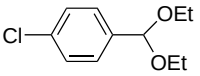
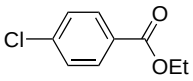
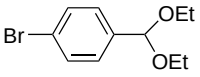
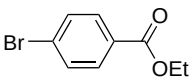
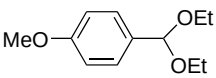
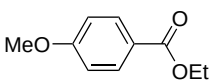
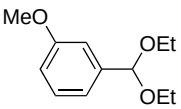
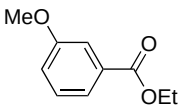
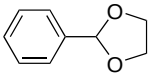
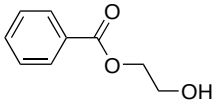
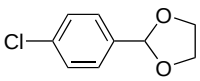
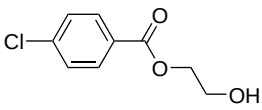
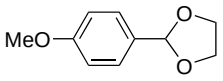
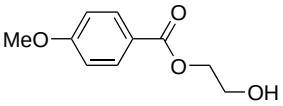
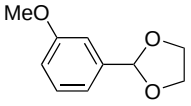
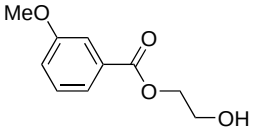
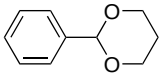
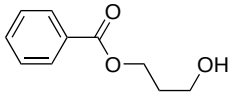
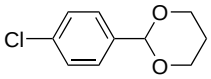
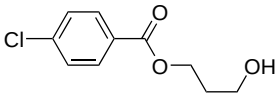
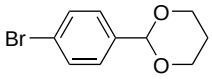
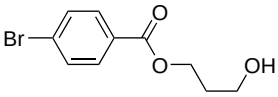
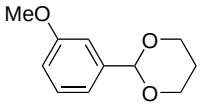
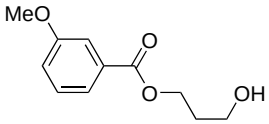
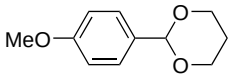
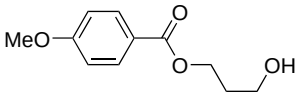
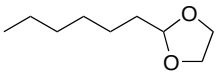
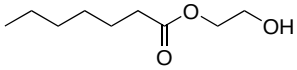
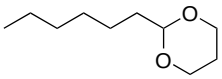
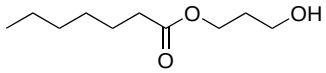
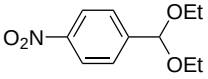
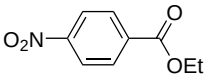
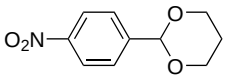
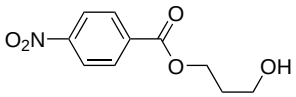
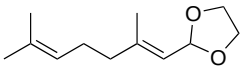
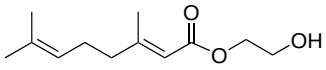
Entry	Substrate	Product	Time (h)	Yield (%)[a,b]
1			20	91
2			20	88
3			8	83
4			8	94
5			8	92
6			10	95
7			10	82
8			8	85

Table 1 Aerobic Oxidation of Acetals to Esters Using NHPI/$Co(OAc)_2$ at Room Temperature (continued)

Entry	Substrate	Product	Time (h)	Yield (%)[a,b]
9			8	88
10			8	94
11			12	84
12			5	89
13			5	92
14			4	89
15			8	91
16			15	89
17			15	94
18			20	no reaction
19			20	no reaction
20			20	34[c,d]

[a] Isolated yields.
[b] The ratios of substrate:NHPI:$Co(OAc)_2$ are 1:0.2:0.01.
[c] The reaction was completed within the indicated time; however, a mixture of unidentified products was formed.
[d] Yield as indicated from the NMR spectrum.

Aerobic Oxidation of Acetals to Esters Using a NHPI/Co(II) System Under O_2 (1 atm); General Procedure

A solution of NHPI (2 mmol, 20 mol%) and $Co(OAc)_2 \cdot 4H_2O$ (0.1 mmol, 1 mol%) in CH_3CN (25 mL) was prepared in a two-necked flask. To this solution the acetal (10 mmol) was added and the resulting pale yellow solution was stirred at r.t. under an oxygen atmosphere (1 atm, balloon filled) for the indicated optimized time (Table 1). After completion of the reaction, the excess of solvent was removed under reduced pressure; the products were purified by chromatography through a short pad of silica gel to give the corresponding ester.

Spectroscopic Details of Selected Products

2-Hydroxyethyl 3-Methoxybenzoate (Table 1, entry 10)

^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC, TMS): δ = 7.57–7.58 (d, *J* = 7.7 Hz, 1 H), 7.50 (s, 1 H), 7.23–7.26 (t, *J* = 7.7 Hz, 1 H), 7.01–7.03 (dd, *J* = 7.7, 2.7 Hz, 1 H), 3.75 (s, 3 H), 3.32 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$, 25 ºC, TMS): δ = 166.89, 159.52, 131.19, 129.44, 122.07, 119.47, 114.31, 66.68, 60.92, 55.41.

3-Hydroxypropyl 4-Bromobenzoate (Table 1, entry 13)
^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC, TMS): δ = 7.78–7.80 (d, *J* = 7.4 Hz, 2 H), 7.47–7.49 (d, *J* = 7.4 Hz, 2 H), 4.38–4.40 (t, *J* = 6.1 Hz, 2 H), 3.70–3.72 (t, *J* = 6.1 Hz, 2 H), 3.13 (br s, 1 H), 1.92–1.97 (quin, *J* = 6.1 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$, 25 ºC, TMS): δ = 166.24, 131.67, 131.10, 129.01, 128.19, 62.29, 58.93, 31.75.

3-Hydroxypropyl 4-Methoxybenzoate (Table 1, entry 15)
^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC, TMS): δ = 7.96–7.98 (d, *J* = 8.9 Hz, 2 H), 6.89–6.91 (d, *J* = 8.9 Hz, 2 H), 4.43–4.45 (t, *J* = 6.2 Hz, 2 H), 3.84 (s, 3 H), 3.74–3.76 (t, *J* = 6.2 Hz, 2 H), 2.44 (br s, 1 H), 1.97–2.00 (q, *J* = 6.2 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$, 25 ºC, TMS): δ = 166.88, 163.51, 131.70, 122.51, 113.70, 61.58, 59.15, 55.49, 32.01.

2-Hydroxyethyl Heptanoate (Table 1, entry 16)
^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC, TMS): δ = 4.13–4.15 (m, 2 H), 3.74–3.76 (m, 2 H), 2.24–2.30 (t, *J* = 7.5 Hz, 2 H), 1.53–1.58 (m, 2 H), 1.37 (br s, 1 H), 1.24 (br m, 6 H), 0.81–0.84 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR(125 MHz, $CDCl_3$, 25 ºC, TMS): δ = 173.56, 65.84, 61.98, 34.16, 31.43, 28.79, 24.83, 22.46, 13.97.

Acknowledgment

The authors thank the Institute for Advanced Studies in Basic Sciences (IASBS) Research Council for support of this work.

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