Room-temperature direct benzylic oxidation catalyzed by cobalt(II) perchlorate

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PII: S0040-4039(16)31363-6
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.10.049
Reference: TETL 48219

To appear in: *Tetrahedron Letters*

Received Date: 8 August 2016
Revised Date: 29 September 2016
Accepted Date: 14 October 2016

Please cite this article as: Yang, Y., Ma, H., Room-temperature direct benzylic oxidation catalyzed by cobalt(II) perchlorate, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.10.049

Tetrahedron Letters
journal homepage: www.elsevier.com

Room-temperature direct benzylic oxidation catalyzed by cobalt(II) perchlorate

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

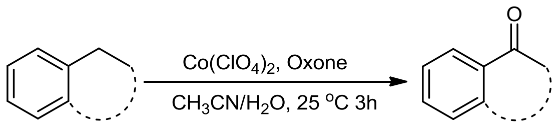
Keywords:
Room temperature
Direct benzylic oxidation
Cobalt(II) perchlorate

ABSTRACT

Aromatic ketones were synthesized from alkylbenzene derivatives through a novel method that employs cobalt(II) perchlorate as catalyst and oxone as oxidant. The reaction smoothly proceeded at room temperature with yields reaching 96%.

The direct oxidation of the benzylic C–H bond is one of the most useful and significant transformations because of its widespread applications, especially in organic synthesis. This attractive synthetic transformation can convert relatively cheap hydrocarbons into value-added hydroxyl and carbonyl compounds, which are important starting materials or intermediates in the synthesis of pharmaceuticals, agrochemicals, and natural products.[1] Traditionally, benzylic oxidation often requires harsh reaction conditions and stoichiometric amounts of metal oxidants, such as potassium permanganate, potassium dichromate, or ammonium cerium nitrate, which generate a large amount of waste.[2] In the past few decades, much effort has been devoted to this transformation; several new metal catalysts[3] involving Cr, Mn, Co, Bi, Ru, Rh, Re, Fe, and Au, as well as metal-free oxidants,[4] such as 2-iodoxybenzoic acid (IBX), NaClO/TBHP, and HBr/H_2O_2, have been developed. Although these methods provided a feasible approach for benzylic oxidation, most of these systems have drawbacks, such as harsh reaction conditions, complicated or expensive metal catalysts, low yield of main product and long reaction time. Therefore, simple and efficient methods for the benzylic C-H oxidation that can operate under mild reaction conditions and use readily available, inexpensive catalysts and non-toxic oxidants are highly desirable.

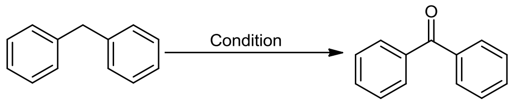
In this paper, we report a new and efficient procedure for the synthesis of benzylic carbonyl compounds from alkyl aromatic compounds by utilizing a readily available and inexpensive transition metal salt, $Co(ClO_4)_2$, with an efficient, inexpensive, versatile, and environmentally benign oxidant, oxone ($KHSO_5$).[5] The direct oxidation of the benzylic C–H bond at room temperature is exploited (Scheme 1).



Scheme 1. Direct benzylic oxidation of alkyl aromatic compounds.

The oxidation of diphenylmethane (**1a**) was chosen as a model reaction to confirm the optimum reaction conditions. The reaction conditions, including the catalysts, oxidants, and solvents, were investigated. The results are summarized in Table 1. Only a trace amount of the product **2a** was obtained when no catalyst was used (Table 1, entry 1). Catalyst screening showed that the yield could be improved with $Co(ClO_4)_2$ as the catalyst; other catalysts, such as $Co(OAc)_2$, $CoCl_2$, $Fe(ClO_4)_3$, and $Cu(ClO_4)_2$, were less effective (Table 1, entries 2–6). Therefore, $Co(ClO_4)_2$ was determined to be the best catalyst. Various oxidants, such as 3-chlorobenzoperoxoic acid (*m*-CPBA), hydrogen peroxide (30% v/v solution of H_2O_2), *tert*-butyl hydroperoxide (70% v/v solution of *t*-BuOOH), *N*-bromosuccinimide (NBS), and O_2 (1 atm) could not improve the product yield (Table 1, entries 4, 7–11). Therefore, oxone was chosen as the ideal oxidant. The reaction was significantly affected by the solvent (Table 1, entries 12–18). Compared with CH_3CN/H_2O mixed solvent, acetonitrile single solvent only afforded a trace amount of the product **2a** (Table 1, entries 12–14), because water plays an important role in the oxidation of benzylic methylenes into ketones.[4e,6] Consequently, the effect of the amount of water in the CH_3CN/H_2O system on the conversion was examined (Table 1, entries 4, 12–15). The results showed that an improved yield could be obtained with CH_3CN/H_2O (1/1, v/v) as the solvent (Table 1, entries 13); other volume ratios of CH_3CN to H_2O were less effective as solvents. Table 1 shows that when acetone /H_2O and AcOH/H_2O were used as solvents instead of CH_3CN/H_2O, the yield of **2a** (Table 1, entries 13, 16–17) was decreased. Therefore, CH_3CN/H_2O (1/1, v/v) was determined to be the best solvent. The effect of the amount of $Co(ClO_4)_2$ and oxone on the oxidation of **1a** was also studied. The results indicated that 0.1 eq $Co(ClO_4)_2$ and 6 eq oxone afforded the oxidation product **2a** with good yield (Table 1, entry 13). Compared with the amount of 0.1 eq, an increase or decrease in the amount of $Co(ClO_4)_2$ reduced the yield of **2a** (Table 1, entries 18–20). When the amount of oxone is less than 6 eq, it results in incomplete reaction, while increasing its amount to 8 eq, may lead to further oxidation of product **2a** (Table 1, entries 21–23). Finally, the optimized catalytic system was obtained, viz., 0.1 eq $Co(ClO_4)_2$ as catalyst, 6.0 eq oxone as oxidant, and CH_3CN/H_2O (1/1, v/v) as solvent at a reaction temperature of 25 °C for a reaction time of 3 h under air (Table 1, entry 13).

Table 1. Screening for optimal reaction conditions.[a]



1a **2a**

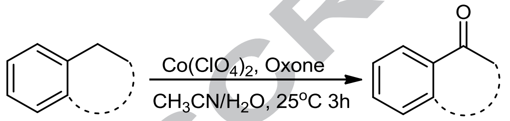
Entry	Catalyst (0.1 eq)	Oxidant (6 eq)	Solvent (v/v)	Yield of **2a** (%)[b]
1	none	Oxone	CH_3CN/H_2O(2/1)	trace
2	$Co(OAc)_2$	Oxone	CH_3CN/H_2O(2/1)	60
3	$CoCl_2$	Oxone	CH_3CN/H_2O(2/1)	48
4	$Co(ClO_4)_2$	Oxone	CH_3CN/H_2O(2/1)	84
5	$Fe(ClO_4)_3$	Oxone	CH_3CN/H_2O(2/1)	9
6	$Cu(ClO_4)_2$	Oxone	CH_3CN/H_2O(2/1)	trace
7	$Co(ClO_4)_2$	*m*-CPBA	CH_3CN/H_2O(2/1)	8
8	$Co(ClO_4)_2$	H_2O_2	CH_3CN/H_2O(2/1)	trace
9	$Co(ClO_4)_2$	*t*-BuOOH	CH_3CN/H_2O(2/1)	trace
10	$Co(ClO_4)_2$	NBS	CH_3CN/H_2O(2/1)	8
11	$Co(ClO_4)_2$	O_2 (1 atm)	CH_3CN/H_2O(2/1)	trace
12	$Co(ClO_4)_2$	Oxone	CH_3CN	trace
13	**$Co(ClO_4)_2$**	**Oxone**	**CH_3CN/H_2O (1/1)**	**96**
14	$Co(ClO_4)_2$	Oxone	CH_3CN/H_2O (1/2)	75
15	$Co(ClO_4)_2$	Oxone	H_2O	6
16	$Co(ClO_4)_2$	Oxone	Acetone /H_2O (1/1)	70
17	$Co(ClO_4)_2$	Oxone	AcOH/H_2O (1/1)	30
18	$Co(ClO_4)_2$ (0.01)	Oxone	CH_3CN/H_2O (1/1)	25
19	$Co(ClO_4)_2$ (0.05)	Oxone	CH_3CN/H_2O (1/1)	27
20	$Co(ClO_4)_2$ (0.15)	Oxone	CH_3CN/H_2O (1/1)	76
21	$Co(ClO_4)_2$	Oxone (2)	CH_3CN/H_2O (1/1)	11
22	$Co(ClO_4)_2$	Oxone (4)	CH_3CN/H_2O (1/1)	58
23	$Co(ClO_4)_2$	Oxone (8)	CH_3CN/H_2O (1/1)	63

[a] Reaction conditions: 1.0 eq of **1a** was stirred at 25 °C for 3 h.

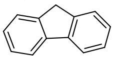
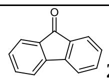
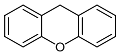
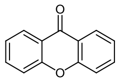
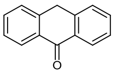
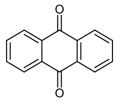
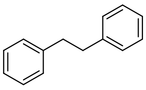
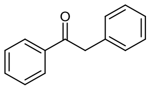
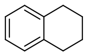
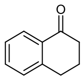
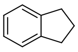
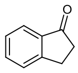
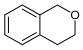
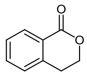
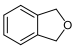
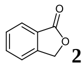
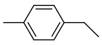
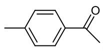
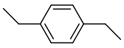
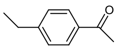
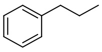
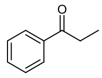
[b] Isolated yield.

Under the optimal reaction conditions, a wide range of benzylic substrates were tested to explore the generality of this oxidation transformation. Table 2 shows that the present protocol was successfully applied to a variety of representative benzylic reagents (Table 2, entries 1–11). The corresponding products were obtained in moderate to excellent yields. The diphenylmethane type substrates could yield the corresponding products with moderate to excellent yields between 62% and 90% (Table 2, entries 1–3). 1,2-Diphenylethane could also afford the corresponding products with moderate yield (Table 2, entry 4). The substrates with one annelated aryl group or one heteroaryl group in a cyclic structure produced the corresponding benzylic oxidation

Table 2. Synthesis of aromatic ketones.[a]



1 **2**

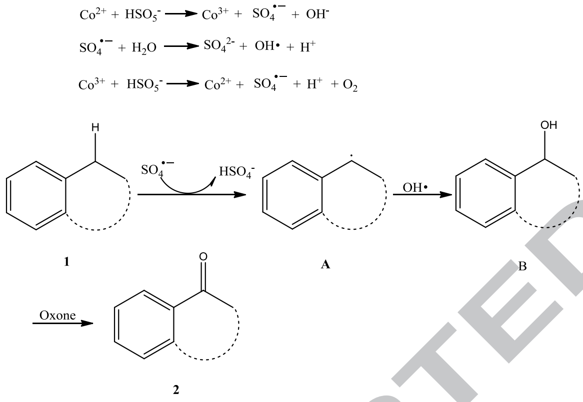
Entry	Substrate (**1**)	Product (**2**)	Yield of **2** (%)[b]
1	 **1b**	 **2b**	90
2	 **1c**	 **2c**	72
3	 **1d**	 **2d**	67
4	 **1e**	 **2e**	78
5	 **1f**	 **2f**	60
6	 **1g**	 **2g**	81
7	 **1h**	 **2h**	66
8	 **1i**	 **2i**	74
9	 **1j**	 **2j**	63
10	 **1k**	 **2k**	65
11	 **1l**	 **2l**	70

[a] Reaction conditions: A mixture of 1 (0.2 mmol), $Co(ClO_4)_2$ (0.02 mmol), oxone (1.2 mmol), CH_3CN (2 mL), and H_2O (2 mL) was stirred in a sealed tube at 25 °C for 3 h.

[b] Isolated yield.

products with moderate to good yields between 60% and 81% (Table 2, entries 5–8). 1,2-Diphenylethane (**1e**), 1,2,3,4-tetrahydronaphthalene (**1f**), 2,3-dihydro-1H-indene (**1g**), isochroman (**1h**), and 1,3-dihydroisobenzofuran (**1i**) have two –CH_2– (methylene) groups attached to the benzene ring, but only one benzyl group can be converted to a carbonyl group. The ethylbenzene derivatives and phenyl propane could be oxidized to form the corresponding ketones with moderate yield (Table 2, entries 9–11). These results clearly showed the generality of the present system.

A plausible mechanism for the the synthesis of **2** is depicted in Scheme 2. Initially, the reactions involve the oxidation of Co^{2+} with oxone to generate a $SO_4^{\bullet-}$ radical in situ. [7] Then the radical reacts with H_2O to provide $OH^{\bullet}$ radical. [8] Followed by the reduction of Co^{3+} with oxone, Co^{2+} is regenerated.[7a] The attack of $SO_4^{\bullet-}$ radical on substrate **1** and subsequent α-H atom abstraction forms species **A**, [9] which further reacts with $OH^{\bullet}$ radical to afford the intermediate **B**. Finally, oxydehydrogenation occurrs, and products (**2**) are formed.[10]



Scheme 2. Proposed mechanism for the synthesis of **2**.

In summary, a mild and efficient methodology for the direct oxidation of the benzylic C–H bond was developed in this study. The reaction can be conducted at room temperature to provide benzylic carbonyl products with moderate to excellent yields. These products are important compounds in the synthesis of pharmaceuticals, agrochemicals, and natural products.

Acknowledgments

This study was supported by the Natural Science Foundation of China (No. 21371079). We also thank the Center for Instrumental Analysis at Jiaxing University, China.

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Graphical Abstract

Room-temperature direct benzylic oxidation catalyzed by cobalt(II) perchlorate

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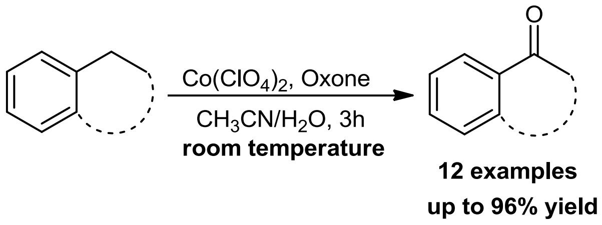
Yiwen Yang *, Hongxia Ma



Highlights

12 aromatic ketones were obtained by the direct benzylic oxidation.

The oxidation can proceed at room temperature and it takes only 3 hours.

It employs $Co(ClO_4)_2$ as catalyst and oxone as oxidant.