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Journal of Inorganic Biochemistry xxx (2015) xxx-xxx



Contents lists available at ScienceDirect

Journal of Inorganic Biochemistry



journal homepage: www.elsevier.com/locate/jinorgbio

Vanadium-catalyzed chlorination under molecular oxygen

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ARTICLE INFO

ABSTRACT

Available online xxxx

Keywords: Vanadium catalyst Chlorination Iodination Molecular oxygen Lewis acid A catalytic chlorination of ketones was performed by using a vanadium catalyst in the presence of Bu₄NI and AlCl₃ under atmospheric molecular oxygen. This catalytic chlorination could be applied to the chlorination of alkenes to give the corresponding *vic*-dichlorides. AlCl₃ was found to serve as both a Lewis acid and a chloride source to induce the facile chlorination. A combination of Bu₄NI and AlI₃ in the presence of a vanadium catalyst under atmospheric molecular oxygen induced the iodination of ketones.

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1. Introduction

Halogenation reaction is one of the most important reactions in the field of organic synthesis, providing versatile precursors and substrates in a variety of coupling reactions. Haloperoxidases are enzymes that catalyze the oxidation of halide ions in the presence of H₂O₂ as an oxidant [1-5]. Haloperoxidases have attracted extensive interest due to their capability to halogenate a range of organic compounds. Various bromination reactions mimicking a catalytic activity of vanadium bromoperoxidase [6], which is a naturally occurring enzyme found in marine algae, have been reported [7–17]. Tungsten [18] or molybdenum [19] complexes have been also demonstrated to serve as a bromination catalyst in the presence of stoichiometric hydrogen peroxide. However, these oxidative bromination systems require a stoichiometric amount of a strong oxidant to generate the bromonium-like species. Some catalytic oxidative bromination reactions with molecular oxygen as a terminal oxidant instead of a strong oxidant have been achieved [20–24]. Recently, we have performed the combination of a vanadium catalyst, a bromide salt, and a Brønsted acid or a Lewis acid in the presence of molecular oxygen induces catalytic oxidative bromination of various arenes, alkenes, alkynes, and ketones without the usage of a strong oxidant [25-27]. These findings prompted us to develop an efficient halogenation method. In this paper, we report the catalytic chlorination reaction of ketones and alkenes without a need of a strong oxidant by using a vanadium catalyst in the presence of Bu₄NI and AlCl₃ with molecular oxygen as a terminal oxidant.

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http://dx.doi.org/10.1016/j.jinorgbio.2015.01.015 0162-0134/© 2015 Elsevier Inc. All rights reserved.

2. Experimental

2.1. General materials and experimental procedures

All reagents and solvents were purchased from commercial sources and were further purified by the standard methods, if necessary. ¹H NMR spectra were recorded in $CDCl_3$ on a JNM-ECS 400 (400 MHz) spectrometer. Chemical shifts were determined by using of tetramethylsilane as an internal standard.

2.2. General procedure for vanadium-catalyzed chlorination under atmospheric molecular oxygen

In a 5 mL three-necked flask, Bu₄NI (111 mg, 0.3 mmol), AlCl₃ (40 mg, 0.3 mmol), and VO(OⁱPr)₃ (15 μ L, 0.063 mmol) were placed. The flask was evacuated and backfilled with molecular oxygen. To the mixture, acetonitrile (1 mL) and a substrate (0.25 mmol) were added. The mixture was stirred at 80 °C under atmospheric molecular oxygen, followed by treatment with 1:1 mixture of saturated Na₂S₂O₃ aqueous solution and saturated NaHCO₃ aqueous solution, and extraction with ether. The organic layer was dried over MgSO₄, filtered, and evaporated. 1,3,5-Trimethoxybenzene or 1,2,4,5-tetramethylbenzene was added as an internal standard, and ¹H NMR analysis was performed to determine an NMR yield. Spectral data of the products were identical with those of commercially available and authentic samples.

2.3. General procedure for vanadium-catalyzed iodination under atmospheric molecular oxygen

In a 5 mL three-necked flask, Bu₄NI (111 mg, 0.3 mmol), AlI₃ (122 mg, 0.3 mmol), and NH₄VO₃ (2.9 mg, 0.025 mmol) were placed. The flask was evacuated and backfilled with molecular oxygen. To the mixture, acetonitrile (1 mL) and a substrate (0.25 mmol) were added.

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T. Moriuchi et al. / Journal of Inorganic Biochemistry xxx (2015) xxx-xxx

Table 3

 Table 1

 Catalytic chlorination of propiophenone by using vanadium catalyst/Bu₄NI/AlCl₃/O₂ system.



Entry	Veat	V cat.	Colu	Time (b)	NMR yield (%)		
	V Cal.	x (mol%)	5017.	Time (II)	2a	3a	
1	NH ₄ VO ₃	10	MeCN	24	60	0	
2	-	-	MeCN	24	0	0	
3 ^a	NH_4VO_3	10	MeCN	24	7	0	
4	NH ₄ VO ₃	10	DME ^b	24	31	0	
5	NH ₄ VO ₃	10	CPME ^c	24	36	0	
6 ^d	NH ₄ VO ₃	10	ether	24	0	0	
7 ^e	NH ₄ VO ₃	10	MeCN	24	64	0	
8	NH ₄ VO ₃	20	MeCN	24	77	0	
9	$VO(O^i Pr)_3$	20	MeCN	24	90	3	
10	VO(acac) ₂	20	MeCN	24	69	9	
11	VOCl ₃	20	MeCN	24	70	0	
12	NH ₄ VO ₃	20	MeCN	36	98	0	

^a Ar atmosphere.

^b 1,2-Dimethoxyethane.

^c Cyclopentyl methyl ether.

^d Room temperature.

e 200 mol% of Bu₄NI and AlCl₃ were used.

The mixture was stirred at 80 °C under atmospheric molecular oxygen, followed by treatment with 1:1 mixture of saturated $Na_2S_2O_3$ aqueous solution and saturated $NaHCO_3$ aqueous solution, and extraction with ether. The organic layer was dried over MgSO₄, filtered, and evaporated. 1,2,4,5-Tetramethylbenzene was added as an internal standard, and ¹H NMR analysis was performed to determine an NMR yield. Spectral data of the products were identical with those of commercially available and authentic samples.

Table 2

The effect of a halide source and aluminium halide in catalytic halogenation of propiophenone by using cat. NH_4VO_3 .



Fraterio		4157	NMR yield (%)		
Entry	Hallue Source	AlY ₃	2a	3a	
1	Bu₄NI	AlCl ₃	60	0	
2	KI	AlCl ₃	7	9	
3	Bu ₄ NCl	All ₃	58	16	
4	Bu ₄ NCl	AlCl ₃	5	0	
5	Bu ₄ NI	All ₃	0	33 ^a	
6 ^b	Bu ₄ NI	All ₃	0	49 ^a	

^a Benzoic acid was obtained as a by-product.
 ^b Reaction time: 48 h.

Catalytic chlorination of ketones by using cat. NH₄VO₃/Bu₄NI/AlCl₃/O₂ system. NH₄VO₃ 20 mol% Bu₄NI 120 mol% AlCl₃ 120 mol% Product



2.4. Gram-scale reaction of propiophenone

In a 50 mL three-necked flask, Bu₄NI (4.43 g, 12 mmol), AlCl₃ (1.60 g, 12 mmol), and VO($O^{i}Pr$)₃ (472 µL, 2.0 mmol) were placed. The flask was evacuated and backfilled with molecular oxygen. To the mixture, aceto-nitrile (30 mL) and propiophenone (1.33 mL, 10 mmol) were added. The mixture was stirred at 80 °C under atmospheric molecular oxygen for 24 h, followed by treatment with 1:1 mixture of saturated Na₂S₂O₃ aqueous solution and saturated NaHCO₃ aqueous solution, and extraction with ether. The organic layer was dried over MgSO₄, filtered, and evaporated. The residue was chromatographed on a silica gel column eluting with hexane and dichloromethane to give 1.32 g (78% yield) of 2-chloro-1-phenylpropan-1-one.

3. Results and discussion

 α -Halocarbonyl compounds are regarded as important precursors for various transformations employed in organic and pharmaceutical syntheses. The chlorination reaction of propiophenone in the presence of 10 mol% of NH₄VO₃, 120 mol% of Bu₄NI, and 120 mol% of AlCl₃ as a Lewis acid in MeCN at 80 °C for 24 h under atmospheric molecular oxygen was performed (Table 1, entry 1). The chlorination reaction proceeded well to afford the α -chlorocarbonyl compound **2a** in 60% yield. No chlorination product was obtained in the absence of NH₄VO₃ (entry 2). This catalytic chlorination reaction was not effectively performed under argon atmosphere (entry 3). The chlorination reaction in other solvents, such as dimethoxyethane (DME), cyclopentyl methyl ether (CPME), and ether resulted in a slightly decreased yield (entries 4-6). The use of 200 mol% of Bu₄NI, and 200 mol% of AlCl₃ did not show a drastically enhanced yield (entry 7). With an increased amount (20 mol%) of NH₄VO₃, the α -chlorocarbonyl derivative **2a** was produced in a good yield (entry 8). Highly active catalysis was observed with $VO(O^{i}Pr)_{3}$ (entry 9) although $VO(acac)_{2}$ and $VOCl_{3}$ exhibited a similar catalytic activity (entries 10–11). The α -chlorocarbonyl compound **2a** was obtained quantitatively by extending the reaction time (entry 12).

2

Please cite this article as: T. Moriuchi, et al., Vanadium-catalyzed chlorination under molecular oxygen, J. Inorg. Biochem. (2015), http://dx.doi.org/10.1016/j.jinorgbio.2015.01.015

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Table 4

Catalytic chlorination of ketones	by	u	ISi	ng	cat.	VO(0	O'Pr)	₃ /Bu ₄ NI/A	lCl_3/O	2 syster	n

Sub

trate	MeCN On	°C Time	FIGUUCI		
	AICI ₃	120	mol%	Product	
	Bu ₄ N	120	mol%		
	VO(0.Pr)3	25	mol%		



The effect of a halide source and aluminium halide in catalytic halogenation of propiophenone by using NH₄VO₃ as a catalyst was examined (Table 2). KI was not effective in the chlorination (entry 2). The combination of Bu₄NCl and All₃ induced the formation of the α chlorination product **2a** in 58% yield together with the α -iodination one **3a** in 16% yield (entry 3). The use of Bu₄NCl and AlCl₃ showed no promising results (entry 4). With Bu₄NI and All₃, the iodination reaction

Table 5

Catalytic chlorination of alkenes by using cat. VO(OⁱPr)₃/Bu₄NI/AlCl₃/O₂ system.

•	VO(O ⁱ Pr) ₃	25	mol%		
Substrate	Bu₄NI AI <mark>CI</mark> ₃	220 220	mol% mol%	via Diable	arida
Substrate -	MeCN, O ₂ ,	80 Âʻ	C, Time	VIC-DICING	Jinde



^a Numbers in parentheses show isolated yields.

proceeded to give **3a** in 33% yield (entry 5). Lewis acidity of AlX₃ and oxidation potentials of halide ions are considered to be key factors in this vanadium-catalyzed chlorination. Extending the reaction time led to a 16% increase in yield (entry 6).

The chlorination reaction of 4'-methoxyacetophenone in the presence of 20 mol% of NH_4VO_3 , 120 mol% of Bu_4NI , and 120 mol% of $AlCl_3$ in MeCN at 80 °C for 36 h under atmospheric molecular oxygen afforded the α -chlorocarbonyl compound **2b** in 49% yield as a major product with the dichlorination product **2bb** in 3% yield (Table 3, entry 1). The longer reaction time led to a slightly increased yield (entry 2). In the case of 4'-chloroacetophenone, the α -chlorination product **2c** was obtained in 55% yield (entry 3). β -Keto esters such as ethyl benzoylacetate underwent the chlorination to give the monochlorinated product **2d** with a trace amount of the monochlorinated product **3d** (entry 4).

A catalytic chlorination of ketones by using cat. VO(OⁱPr)₃/Bu₄NI/ AlCl₃/O₂ system was examined (Table 4). The chlorination reaction of 4'-methoxyacetophenone proceeded to afford the α -chlorination product **2b** in a moderate yield and the dichlorination product **2bb** in 13% yield with a trace amount of the α -iodination product **3b** (entry 1). VO(OⁱPr)₃ showed higher efficiency than NH₄VO₃. 4'-Chloroacetophenone was chlorinated to give the monochlorinated product 2c in 66% yield and the dichlorination product **2cc** in 13% yield together with a small amount of the α -iodinated product **3c** (entry 2). Starting from acetophenone, the α -chlorinated product **2e** was obtained in 84% yield with the dichlorinated product **2ee** in 12% yield and a small amount of the α iodinated product 3e (entry 3). This catalytic chlorination could be applied to the chlorination of alkenes (Table 5). 1-Decene underwent the selective vic-chlorination to afford 1,2-dichlorodecane (5a) in 72% yield (entry 1). Catalytic chlorination of 5-hexene-1-ol proceeded smoothly to give the dichlorinated product 5b in 78% yield with the hydroxy group intact (entry 2). Allylbenzene was converted into the dichloride in 87% yield (entry 3).

It is noteworthy to mention that a gram-scale reaction underwent successfully to give the expected chlorinated product in a high yield, as exemplified by the α -chlorination of propiophenone in 78% isolated yield as shown in Scheme 1. Starting from the α -iodo ketone **3a**, the α -chloro ketone **2a** was obtained as a sole product selectively (Scheme 2). Thus, the key intermediate for the chlorination is proposed to be the α -iodo ketone **3a**, which is considered to be generated by the oxidation of an iodide ion via oxygen-atom transfer of an oxovanadium species activated by a Lewis acid [26,27].

4. Conclusions

The catalytic chlorination reaction of ketones without the use of a strong oxidant was achieved by using a commercially available inexpensive ligand-free vanadium catalyst in the presence of Bu₄NI and AlCl₃ with molecular oxygen as a terminal oxidant, in which AlCl₃ was found to serve as both a Lewis acid and a chloride source to induce the facile chlorination. This catalytic system was also demonstrated to be capable of inducing the catalytic chlorination of Bu₄NI and AlI₃ in the presence of a vanadium catalyst under atmospheric molecular oxygen was found to induce the iodination of ketones. Studies on the reaction mechanism and synthetic versatility, and application of this practical method to other reactions are now in progress.

Acknowledgment

This work was supported partly by a Grant-in-Aid for Scientific Research ACT-C program of the Japan Science and Technology Agency (JST). Thanks are due to the Analytical Center, Graduate School of Engineering, Osaka University. The donation of VO(OⁱPr)₃ from the Nichia corporation is also acknowledged.

Please cite this article as: T. Moriuchi, et al., Vanadium-catalyzed chlorination under molecular oxygen, J. Inorg. Biochem. (2015), http://dx.doi.org/10.1016/i.jinorgbio.2015.01.015

ARTICLE IN PRESS

T. Moriuchi et al. / Journal of Inorganic Biochemistry xxx (2015) xxx-xxx



Scheme 1. Gram-scale chlorination of propiophenone.



Scheme 2. Catalytic chlorination reaction of 2-iodo-1-phenylpropan-1-one.

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4

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