



Vanadium-catalyzed oxidative aromatization of 2-cyclohexenones under molecular oxygen

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ABSTRACT

An efficient catalytic oxidative aromatization of 2-cyclohexenones was achieved by a combination of a commercially available inexpensive ligand-free vanadium catalyst, a bromide source, and an acid under atmospheric oxygen to afford the corresponding phenol derivatives. This catalytic oxidative aromatization proceeded even under air. Furthermore, a gram-scale reaction was performed successfully.

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Oxidative transformation of organic molecules constitutes a fundamental and important reaction.¹ Dehydrogenative aromatization is one of the most important oxidative transformations in organic synthesis.^{1,2} Some methods for catalytic dehydrogenative aromatization of α,β -unsaturated cyclohexenones to phenols have been reported.³ These catalytic systems, however, require severe conditions or a long reaction time. In a previous letter, Lewis acid, $\text{VO}(\text{OR})\text{Cl}_2$, with oxidation capability has been reported to induce the oxidative aromatization of α,β -unsaturated cyclohexenones to aryl ethers.⁴ This system, however, requires a stoichiometric amount of the oxidant. Catalytic processes using molecular oxygen as a terminal oxidant are desirable from the viewpoint of environmentally benign synthesis. We have already demonstrated that the aerobic vanadium-catalyzed oxidative bromination reaction of arenes, alkenes, and alkynes is achieved by using a commercially available inexpensive ligand-free vanadium catalyst, a bromide ion source, and an acid under atmospheric oxygen or air, wherein a brominium cation-like species is proposed to be a key intermediate.⁵ These results prompted us to investigate a catalytic scope of the vanadium-catalyzed oxidation system. We herein report the vanadium-catalyzed oxidative aromatization of 2-cyclohexenones to phenols under molecular oxygen.

The oxidative aromatization reaction of 2-cyclohexen-1-one (**1a**) with 5 mol % of NH_4VO_3 , 300 mol % of Bu_4NBr , and 300 mol % of trifluoroacetic acid (TFA) was performed at 80 °C in 1,4-dioxane under atmospheric oxygen for 6 h (Table 1). The oxidative aromatization proceeded smoothly to afford phenol (**2aa**) in 80% yield with the concomitant formation of *p*-benzoquinone in 7% yield (Table 1, entry 1). The reaction without NH_4VO_3 catalyst gave only a trace amount of **2aa** (entry 2). No aromatization product was obtained in the absence of Bu_4NBr or TFA (entries 3 and 4). NH_4VO_3 did not

operate as a catalyst under argon atmosphere (entry 5), indicating that molecular oxygen is essential for an efficient catalytic oxidative-aromatization reaction. NaVO_3 was found to be less effective than NH_4VO_3 (entry 6). V_2O_5 was not effective in the oxidative aromatization (entry 7). High catalytic activity was observed with VOSO_4 to give the further monobrominated product **2ab** (entry 8) although the oxidative aromatization was not effectively performed under argon atmosphere (entry 9). With VOSO_4 , the reaction proceeded smoothly in 4 h (entry 10). The catalytic oxidative aromatization was effectively performed even under air to afford 75% of **2aa** although a longer reaction time was required (entries 11 and 12). $\text{VO}(\text{acac})_2$ exhibited a similar catalytic activity (entry 13). The oxo metal complexes, $(\text{NH}_4)_2\text{MoO}_4$ and NH_4ReO_4 displayed no promising results (entries 14 and 15). The catalytic oxidative aromatization of 3,5-dimethyl-2-cyclohexen-1-one (**1b**) with 5 mol % of NH_4VO_3 , 1000 mol % of Bu_4NBr , and 1000 mol % of TFA led to the formation of 2,4,6-tribromo-3,5-dimethylphenol (**2bb**) in 73% isolated yield (Scheme 1).



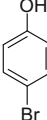
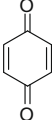
The catalytic oxidative aromatization of **1a** also proceeded moderately by a combination of 5 mol % of VOSO_4 and 300 mol % of HBr aq (48%), indicating that HBr serves as both a bromide source and Brønsted acid (Table 2, entry 1). Furthermore, the amount of HBr aq (48%) could be reduced to 50 mol % to give phenol (**2aa**) in 77% yield although a longer reaction time, 9 h, was required (entry 2). The oxidatively aromatized product **2aa** could also be obtained even under air with a long reaction time (entries 3 and 4). Catalytic activity of other catalysts was surveyed using these conditions. $\text{VO}(\text{acac})_2$ and NH_4VO_3 could be also effective as a vanadium catalyst (entries 5 and 6). NaVO_3 , V_2O_5 , and $\text{VO}(\text{O}^i\text{Pr})_3$ exhibited less effective catalytic activities than VOSO_4 (entries 7, 8, and 9). $(\text{NH}_4)_2\text{MoO}_4$ showed no promising result (entry 10) although a moderate catalytic activity was observed with NH_4ReO_4 (entry 11).

The reaction of 4-carbethoxy-3-methyl-2-cyclohexen-1-one (**1c**) with 5 mol % of VOSO_4 , 300 mol % of Bu_4NBr , and 300 mol % of TFA resulted in the efficient catalytic oxidative aromatization

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Table 1
Catalytic oxidative aromatization of **1a**

	Cat. Br ⁻ source Acid	5 mol% 300 mol% 300 mol%		+		+	
1a	1,4-Dioxane, O ₂ , 80 °C, 6 h		2aa		2ab		3
Entry	Cat.	Br ⁻ source	Acid ^a	NMR yield (%)			
				2aa	2ab	3	
1	NH ₄ VO ₃	Bu ₄ NBr	TFA	80	0	7	
2	—	Bu ₄ NBr	TFA	3	0	1	
3 ^b	NH ₄ VO ₃	—	TFA	0	0	0	
4	NH ₄ VO ₃	Bu ₄ NBr	—	0	0	0	
5 ^c	NH ₄ VO ₃	Bu ₄ NBr	TFA	6	0	1	
6	NaVO ₃	Bu ₄ NBr	TFA	67	0	6	
7	V ₂ O ₅	Bu ₄ NBr	TFA	25	0	Trace	
8	VOSO ₄	Bu ₄ NBr	TFA	64	24		4
9 ^c	VOSO ₄	Bu ₄ NBr	TFA	4	0	1	
10 ^d	VOSO ₄	Bu ₄ NBr	TFA	75	4	6	
11 ^e	VOSO ₄	Bu ₄ NBr	TFA	45	0	9	
12 ^f	VOSO ₄	Bu ₄ NBr	TFA	75	0	14	
13	VO(acac) ₂	Bu ₄ NBr	TFA	86	0	6	
14 ^g	(NH ₄) ₂ MoO ₄	Bu ₄ NBr	TFA	16	0	3	
15 ^g	NH ₄ ReO ₄	Bu ₄ NBr	TFA	0	0	0	

^a TFA = trifluoroacetic acid.

^b Ethylene glycol diformate was obtained as a by-product.

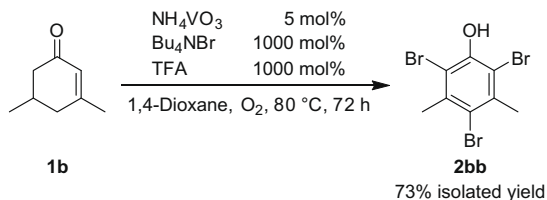
^c Under argon atmosphere.

^d 4 h.

^e Under air.

^f Under air for 21 h.

^g 24 h.



Scheme 1. Oxidative aromatization of **1b** catalyzed by NH₄VO₃.

to give the phenol derivative **2c** in 91% yield (Table 3, entry 1). Furthermore, the catalytic oxidative aromatization was also effectively performed even under air to afford 92% of **2c** although a longer reaction time was required (entry 2). The oxidatively aromatized product **2c** could be produced by the combination of 5 mol % of VOSO₄ and 50 mol % of HBr aq (48%) under both oxygen atmosphere and air (entries 3 and 4).

It should be noted that the catalyst loading could be successfully reduced to 1 mol % in a gram-scale reaction for the catalytic oxidative aromatization of **1c** to afford **2c** in 81% isolated yield, as shown in Scheme 2.⁶ With the combination of 5 mol % of VOSO₄ and 50 mol % of HBr aq (48%), 1.27 g (71% yield) of the aromatized product **2c** was isolated.

In conclusion, the combination of a commercially available inexpensive ligand-free vanadium catalyst, a bromide source, and an acid under atmospheric oxygen was demonstrated to provide a versatile synthetic method for the catalytic oxidative aromatization of 2-cyclohexenones, affording the corresponding phenol derivatives. This catalytic oxidative aromatization could be performed even under air. Furthermore, a gram-scale reaction successfully proceeded to give the desired product. Further investigations on the applica-

Table 2
Catalytic oxidative aromatization of **1a** by using HBr aq (48%) as proton and bromide sources

Entry	Cat.	NMR yield (%)			
		2aa	2ab	3	
1 ^a	VOSO ₄	54	0	15	
2	VOSO ₄	77	0	10	
3 ^b	VOSO ₄	32	0	4	
4 ^c	VOSO ₄	73	0	10	
5	VO(acac) ₂	72	0	8	
6	NH ₄ VO ₃	71	0	5	
7	NaVO ₃	46	0	4	
8	V ₂ O ₅	64	0	7	
9	VO(O ⁱ Pr) ₃	57	0	8	
10	(NH ₄) ₂ MoO ₄	30	0	2	
11	NH ₄ ReO ₄	59	0	31	

^a With 300 mol % of HBr aq (48%) for 6 h.

^b Under air.

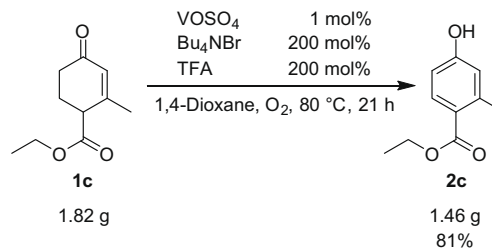
^c Under air for 47 h.

Table 3
Oxidative aromatization of **1c** catalyzed by VOSO₄

Entry	Br ⁻ /acid ^a source	x mol %	Atom sphere	Time (h)	NMR yield (%) 2c
1	Bu ₄ NBr/TFA	300/ 300	O ₂	9	91 ^b
2	Bu ₄ NBr/TFA	300/ 300	Air	14	92
3	HBr aq (48%)	50	O ₂	15	86
4	HBr aq (48%)	50	Air	18	82

^a TFA = trifluoroacetic acid.

^b Isolated yield is 89%.



Scheme 2. Gram-scale catalytic oxidative aromatization of **1c** catalyzed by VOSO₄.

tion of the catalytic oxidation system to other reactions and the reaction mechanism are now in progress.

Acknowledgments

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Supplementary data

Supplementary data (general information, procedure, and NMR spectral data) associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2009.10.070](https://doi.org/10.1016/j.tetlet.2009.10.070).

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6. *Gram-scale catalytic oxidative aromatization of 4-carbethoxy-3-methyl-2-cyclohexen-1-one (1c) catalyzed by VOSO₄*: In a 50 mL two-necked flask equipped with a reflux condenser, vanadium(IV) oxide sulfate hydrate (22.6 mg, 0.10 mmol) and tetrabutylammonium bromide (6.45 g, 20 mmol) were placed. The flask was evacuated and backfilled with atmospheric oxygen. To the mixture, 1,4-dioxane (20 mL), 4-carbethoxy-3-methyl-2-cyclohexen-1-one (1.82 g, 10 mmol), and trifluoroacetic acid (1.5 mL, 10 mmol) were added. The mixture was stirred at 80 °C for 21 h. The mixture was diluted with ether, then treated with deionized water, and was extracted three times with ether. The organic layer was dried over MgSO₄, filtered, and evaporated. The product was isolated by column chromatography (SiO₂, hexane/AcOEt = 1:1 v/v) to give 1.46 g of ethyl-4-hydroxy-2-methylbenzoate (**2c**, 81%).