



## Direct conversion of benzylamines to imines via atmospheric oxidation in the presence of VO(Hhpic)<sub>2</sub> catalyst

Shintaro Kodama<sup>a</sup>, Jun Yoshida<sup>a</sup>, Akihiro Nomoto<sup>a,\*</sup>, Yukihiro Ueta<sup>a</sup>, Shigenobu Yano<sup>b</sup>, Michio Ueshima<sup>a</sup>, Akiya Ogawa<sup>a,\*</sup>

<sup>a</sup> Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University, 1-1 Gakuen-cho, Nakaku, Sakai, Osaka 599-8531, Japan

<sup>b</sup> Endowed Research Section, Photomedical Science, Innovative Collaboration Center, Kyoto University, Kyoto 615-8250, Japan

### ARTICLE INFO

#### Article history:

Received 28 December 2009

Revised 20 February 2010

Accepted 25 February 2010

Available online 3 March 2010

#### Keywords:

Oxidation reaction

Vanadium catalyst

Amines

Atmospheric oxygen

### ABSTRACT

Oxovanadium complex bearing 3-hydroxypicolinic acid (H<sub>2</sub>hpic), that is, VO(Hhpic)<sub>2</sub>, successfully catalyzes a highly selective oxidation of benzylamines to the corresponding *N*-(benzylidene)benzylamines under atmospheric molecular oxygen. In addition, the use of imidazolium-type ionic liquids as solvent makes it possible to attain recycling of the catalyst.

© 2010 Elsevier Ltd. All rights reserved.

Catalytic oxidation reactions of organic compounds with the aid of molecular oxygen as the primary oxidant have attracted much attention from a green chemical viewpoint in recent years.<sup>1</sup> In particular, considerable efforts have been devoted to accomplish the oxidation of alcohols to carbonyl compounds. By contrast, the corresponding amine to imine conversion by oxidation has remained largely undeveloped, despite great utility of imines in the synthesis of industrial materials and biologically active compounds, such as amides, chiral amines, oxazolindines, hydroxyamines, and nitrones.<sup>2</sup> Since the oxidation of primary amines generally leads to other nitrogen containing compounds, such as nitriles,<sup>3</sup> it is of great importance to develop the catalytic oxidation of the primary amines to the corresponding imines using molecular oxygen.<sup>4</sup> Direct synthesis of imines from the primary amines by oxidation offers an alternative synthetic route to the condensation of an amine with a carbonyl compound.

Herein, we wish to report the selective oxidation of benzylamines to produce directly the corresponding *N*-(benzylidene)benzylamine derivatives catalyzed by an oxovanadium complex bearing 3-hydroxypicolinic acid (H<sub>2</sub>hpic), that is, VO(Hhpic)<sub>2</sub> (Fig. 1), under the atmosphere of molecular oxygen.<sup>5,6</sup>

We first examined reactions of benzylamine **1a** with vanadium catalysts under the atmosphere of molecular oxygen in acetonitrile (Table 1).<sup>7</sup> Among the catalysts employed, VO(Hhpic)<sub>2</sub> was found to be the most effective catalyst for converting benzylamine **1a** to *N*-(benzylidene)benzylamine **2a** (entry 1). General vanadium

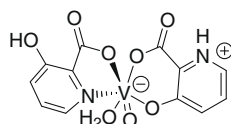
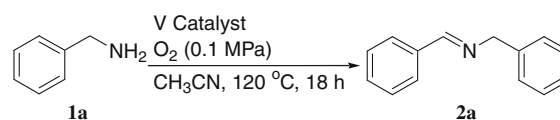


Figure 1. Structure of VO(Hhpic)<sub>2</sub>.

Table 1  
Oxidation of benzylamine with vanadium catalysts<sup>a</sup>



Entry	V Catalyst	Mol %	Yield <sup>b</sup> (%) <b>2a</b>	Recovery <sup>b</sup> (%) <b>1a</b>
1	VO(Hhpic) <sub>2</sub>	2	86	Trace
2	VO(acac) <sub>2</sub>	2	34	45
3	V <sub>2</sub> O <sub>5</sub>	1	30	52
4	VOSO <sub>4</sub>	2	30	43
5	None			No reaction

<sup>a</sup> Reactions were carried out on 1.5 mmol scale in a stainless autoclave with stirring under oxygen (0.1 MPa).

<sup>b</sup> Determined by <sup>1</sup>H NMR.

\* Corresponding authors. Tel./fax: +81 72 254 9290 (A.O.).  
E-mail address: ogawa@chem.osakafu-u.ac.jp (A. Ogawa).

**Table 2**  
Oxidation of amine derivatives<sup>a</sup>

Entry	Substrate	Product	Time (h)	Yield <sup>b</sup> (%)
1	Ar=C <sub>6</sub> H <sub>5</sub> <b>1a</b>	<b>2a</b>	18	86 <sup>c</sup>
2	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> <b>1b</b>	<b>2b</b>	24	70
3	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> <b>1c</b>	<b>2c</b>	18	72 <sup>c</sup>
4	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> <b>1d</b>	<b>2d</b>	24	71
5			42	37 <sup>c,d</sup>
6			18	78
7			24	75

<sup>a</sup> Reactions were carried out using 1.5 mmol of substrate, 10.3 mg (0.03 mmol) of VO(Hhpic)<sub>2</sub>, and 6 mL of acetonitrile in a stainless autoclave with stirring at 120 °C under 0.1 MPa of oxygen for appropriate times.

<sup>b</sup> Isolated yield.

<sup>c</sup> Determined by <sup>1</sup>H NMR.

<sup>d</sup> The starting material (58%) was recovered.

catalysts in oxidation reactions such as VO(acac)<sub>2</sub> and V<sub>2</sub>O<sub>5</sub> had less catalytic activity (entries 2 and 3). In the case of VOSO<sub>4</sub>, which is the starting material of VO(Hhpic)<sub>2</sub>, **2a** was formed in a low yield under the same condition (entry 4).

Results of the oxidation of various benzylamine derivatives using VO(Hhpic)<sub>2</sub> are shown in Table 2. Oxidations of *p*-substituted benzylamine derivatives **1a–d** proceeded successfully to afford the corresponding imines **2a–d** (entries 1–4). As to the oxidation of the secondary amines (entries 5 and 6), dibenzylamine **1e** was oxidized to the corresponding imine **2e** in a moderate yield (entry 5). On the other hand, 1,2,3,4-tetrahydroisoquinoline **1f** was selectively dehydrogenated to 3,4-dihydroisoquinoline **2f** (entry 6). Interestingly, the oxidation of tertiary amine **1g** proceeded to afford *N*-(benzylidene)aniline **2g** in a good yield via the elimination of a benzyl group (benzaldehyde (75%, <sup>1</sup>H NMR yield) was formed as a byproduct) (entry 7).<sup>8</sup>

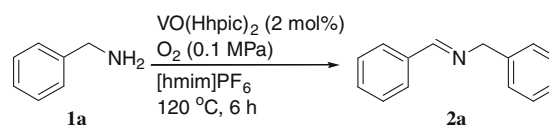
Based on our interest in green chemistry, we next examined the present oxidation of amines to imines using ionic liquid (IL) as an eco-friendly solvent. IL has a nature of reasonable thermal and

**Table 3**  
Oxidation of benzylamines in ionic liquids<sup>a</sup>

Entry	Substrate	Ionic liquid	Yield <sup>b</sup> (%)
1		Me-N <sup>+</sup> (Me)N <sup>+</sup> Hex <sup>-</sup> PF <sub>6</sub> <sup>-</sup>	75
2	<b>1a</b>	Me-N <sup>+</sup> (Me)N <sup>+</sup> Bu <sup>-</sup> PF <sub>6</sub> <sup>-</sup>	46
3		Me-N <sup>+</sup> (Me)N <sup>+</sup> Bu <sup>-</sup> BF <sub>4</sub> <sup>-</sup>	43
4		Me-N <sup>+</sup> (Me)N <sup>+</sup> Et <sup>-</sup> BF <sub>4</sub> <sup>-</sup>	18
5		Me-N <sup>+</sup> (Me)N <sup>+</sup> Hex <sup>-</sup> PF <sub>6</sub> <sup>-</sup>	73

<sup>a</sup> All reactions were carried out in 1.5 mmol scale using a glass vessel filled with O<sub>2</sub>.

<sup>b</sup> Determined by <sup>1</sup>H NMR.

**Table 4**  
Recycling study of VO(Hhpic)<sub>2</sub> in ionic liquid<sup>a</sup>

Run	1st	2nd	3rd	4th	5th	6th	7th	8th	9th
Yield <sup>b,c</sup> (%)	69	70	64	67	68	66	56	58	68 (67) <sup>d</sup>

<sup>a</sup> The reaction was carried out with benzylamine (1.5 mmol), and VO(Hhpic)<sub>2</sub> (0.3 mmol) dissolved in [hmim]PF<sub>6</sub> (2 mL) in a 30 mL two-necked round-bottomed flask with stirring under atmospheric oxygen (for 1st). After extraction with Et<sub>2</sub>O, benzylamine was then added to the resulting ionic liquid phase containing the catalyst (for the other runs).

<sup>b</sup> The starting benzylamine still remained, but no byproduct was detected.

<sup>c</sup> Determined by <sup>1</sup>H NMR.

<sup>d</sup> Isolated yield.

chemical stability, negligible vapor pressure, non-flammability, and high capacity to dissolve various organic and inorganic compounds.<sup>9–11</sup>

The results of the oxidation using ILs in a glass vessel are summarized in Table 3.<sup>12</sup> We first conducted the oxidation of **1a** using 1-hexyl-3-methylimidazolium hexafluorophosphate, [hmim]PF<sub>6</sub>, as a solvent. As a result, the oxidation product **2a** was obtained in 75% yield (entry 1). On the other hand, other ILs bearing different alkyl chain or counter anion were less effective, resulting moderate to low yields of **2a** (entries 2–4).<sup>13,14</sup> When we conducted the oxidation of **1b** using [hmim]PF<sub>6</sub>, the product **2b** was formed in 73% yield.

Next, recycling feature of the catalyst in [hmim]PF<sub>6</sub> was demonstrated, as shown in Table 4. After extraction with diethyl ether to separate the products from the IL, the IL containing the catalyst was dried in vacuo for 6 h, and the resulting ionic liquid layer was used for the oxidation reaction. The result shows that [hmim]PF<sub>6</sub> containing VO(Hhpic)<sub>2</sub> was successfully reused for further eight runs without any detectable loss in catalytic activity.

In summary, we have found that VO(Hhpic)<sub>2</sub> is a highly effective catalyst for selective oxidation of benzylamines to the corresponding imines by molecular oxygen in acetonitrile. In addition, VO(Hhpic)<sub>2</sub> in ionic liquids could be employed as a reusable catalyst for the oxidation of benzylamines to imines. Further studies of the oxidation using ionic liquids are in progress. Results will be reported in due course.

## Acknowledgments

This research was supported by JST Research Seeds Quest Program (Lower Carbon Society), from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and Kansai Research Foundation for Technology Promotion (KRF). S.K. acknowledges Research Fellowships of the Japan Society for the Promotion of Science (JSPS) for Young Scientists.

## Supplementary data

Experimental procedures, compound characterization, and selected  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectral data are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.150.

## References and notes

- (a) Murahashi, S.-I.; Komiya, N. In *Modern Oxidation Methods*; Bäckvall, J.-E., Ed.; Wiley-VCH: Weinheim, 2004; Chapter 6, pp. 165–191; (b) Hudlický, M. *Oxidation in Organic Chemistry*; ACS Monograph 186; American Chemical Society: Washington, DC, 1990; (c) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidation of Organic Compounds*; Academic Press: New York, 1981; (d) Mizuno, N.; Kamata, K.; Uchida, S.; Yamaguchi, K. In *Modern Heterogeneous Oxidation Catalysis*; Mizuno, N., Ed.; Wiley-VCH: Weinheim, 2009; Chapter 6, pp. 185–216; (e) Punta, C.; Moscatelli, D.; Porta, O.; Minisci, F.; Gambarotti, C.; Lucarini, M. In *Mechanism in Homogeneous and Heterogeneous Epoxidation Catalysis*; Oyama, S. T., Ed.; Elsevier: Amsterdam, 2008; Chapter 6, pp. 217–229; (f) Conte, V.; Floris, B.; Silvagni, A. In *Vanadium: The Versatile Metal*; Kustin, K., Pessoa, J. C., Crans, D. C., Eds.; ACS Symposium Series 974; American Chemical Society: Washington, DC, 2007; Chapter 2, pp. 28–37.
- (a) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247; (b) Vilaivan, T.; Winotapan, C.; Banphavichit, V.; Shinada, T.; Ohfuné, Y. *J. Org. Chem.* **2005**, *70*, 3464; (c) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407; (d) Bishop, M. J.; McNutt, R. W. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1311; (e) Martiny, L.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 699.
- (a) Li, F.; Chen, J.; Zhang, Q.; Wang, Y. *Green Chem.* **2008**, *10*, 553; (b) Kim, J. W.; Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 9249; (c) Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 1480; (d) Maeda, Y.; Nishimura, T.; Uemura, S. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2399; (e) Mori, K.; Yamaguchi, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Chem. Commun.* **2001**, 461; (f) Bailey, A. J.; James, B. R. *Chem. Commun.* **1996**, 2343.
- (a) Grierrane, A.; Corma, A.; Garcia, H. J. *Catal.* **2009**, *264*, 138; (b) Aschwanden, L.; Mallat, T.; Krumeich, F.; Baiker, A. *J. Mol. Catal. A: Chem.* **2009**, *309*, 57; (c) Zhu, B.; Lazar, M.; Trewyn, B. G.; Angelici, R. J. *J. Catal.* **2008**, *260*, 1; (d) Landge, S. M.; Atanassova, V.; Thimmaiah, M.; Török, B. *Tetrahedron Lett.* **2007**, *48*, 5161; (e) Hirao, T.; Fukuhara, S. *J. Org. Chem.* **1998**, *63*, 7534; (f) Higuchi, M.; Ikeda, I.; Hirao, T. *J. Org. Chem.* **1997**, *62*, 1072; (g) Nakayama, K.; Hamamoto, M.; Nishiyama, Y.; Ishii, Y. *Chem. Lett.* **1993**, 1699; (h) Hirao, T.; Higuchi, M.; Ohshiro, Y.; Ikeda, I. *Chem. Lett.* **1993**, 1889; (i) Neumann, R.; Levin, M. *J. Org. Chem.* **1991**, *56*, 5707.
- Nakai, M.; Obata, M.; Sekiguchi, F.; Kato, M.; Shiro, M.; Ichimura, A.; Kinoshita, I.; Mikuriya, M.; Inohara, T.; Kawabe, K.; Sakurai, H.; Orvig, C.; Yano, S. *J. Inorg. Biochem.* **2004**, *98*, 105.
- We have reported that VO(Hhpic)<sub>2</sub> has a catalytic activity for the oxidation of benzyl alcohols with molecular oxygen: Kodama, S.; Ueta, Y.; Yoshida, J.; Nomoto, A.; Yano, S.; Ueshima, M.; Ogawa, A. *Dalton Trans.* **2009**, 9708.
- General procedure for the oxidation of benzylamines using an autoclave or sealed tube* (Table 1): The vanadium complex (0.03 mmol, 10.3 mg), amine (1.5 mmol), and acetonitrile (6 mL) were placed in a 50 mL autoclave in sequence, and then oxygen was introduced (0.1 MPa). This autoclave was then put into an oil bath (120 °C) under magnetic stirring for the desired reaction time. The resulting mixture was filtered through a Celite pad. After evaporation of the solvent, the product was purified by column chromatography on silica gel using ethyl acetate and hexane as eluent to afford the analytically pure imines.
- Similar conditions could not be employed with simple aliphatic amines such as aminomethylcyclohexane and di-*n*-hexylamine, and further detailed optimization of the conditions is required for the oxidation of them.
- (a) For reviews concerning catalytic reactions using ionic liquids, see: Wasserscheid, P.; Schulz, P. In *Ionic Liquids in Synthesis*; 2nd ed.; Wasserscheid, P., Welton, T., Eds.; Wiley-VCH: Weinheim, 2008; pp. 369–463. Chapter 5.3; (b) Muzart, J. *Adv. Synth. Catal.* **2006**, *348*, 275; (c) Fei, Z.; Geldbach, T. J.; Zhao, D.; Dyson, P. J. *Chem. Eur. J.* **2006**, *12*, 2122; (d) Miao, W.; Chan, T. H. *Acc. Chem. Res.* **2006**, *39*, 897; (e) Jain, N.; Kumar, A.; Chauhan, S.; Chauhan, S. M. S. *Tetrahedron* **2005**, *61*, 1015; (f) Baudequin, C.; Brégeon, D.; Levillain, J.; Guillen, F.; Plaquevent, J.-C.; Gaumont, A.-C. *Tetrahedron: Asymmetry* **2005**, *16*, 3921; (g) Welton, T. *Coord. Chem. Rev.* **2004**, *248*, 2459; (h) Sheldon, R. *Chem. Commun.* **2001**, 2399; (i) Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667.
- Catalytic oxidation of alcohols in ILs: (a) Chhikara, B. S.; Chandra, R.; Tandon, V. *J. Catal.* **2005**, *230*, 436; (b) Ansari, I. A.; Gree, R. *Org. Lett.* **2002**, *4*, 1507; (c) Wolfson, A.; Wuyts, S.; De Vos, D. E.; Vankelecom, I. F. J.; Jacobs, P. A. *Tetrahedron Lett.* **2002**, *43*, 8107.
- Ragauskas and co-workers reported selective aerobic oxidation of alcohols using vanadium catalysts in IL: Jiang, N.; Ragauskas, A. J. *Tetrahedron Lett.* **2007**, *48*, 273.
- General procedure for the oxidation of benzylamines in [hmim]PF<sub>6</sub>* (Table 3): In a 30 mL two-necked round-bottomed flask with a stirring bar under atmosphere of oxygen, VO(Hhpic)<sub>2</sub> (0.03 mmol, 10.3 mg), amine (1.5 mmol), and [hmim]PF<sub>6</sub> (2 mL) were placed, and then the mixture was heated at 120 °C for the appropriate time with magnetic stirring. The resulting mixture was extracted with diethyl ether. The extracts were concentrated in vacuo. The product was confirmed by  $^1\text{H}$  NMR spectroscopy. Purification of the product by column chromatography on silica gel using ethyl acetate and hexane as eluent afforded the analytically pure imines.
- Although other ionic liquids, such as [hmim]Cl, [bmim]Tf<sub>2</sub>N, and [edimim]Tf<sub>2</sub>N (Tf<sub>2</sub>N: bis(trifluoromethanesulfonyl)imide), were employed for this reaction, the separation of the product from these ionic liquids was relatively difficult, compared with the oxidation in [hmim]PF<sub>6</sub>.
- The yields of the product are increased by lengthening the alkyl group of ionic liquids (Table 3). The lipophilicity of the ionic liquids rises as the alkyl chain of ionic liquids extends, and therefore, the solubility of the substrate in the ionic liquid increases. As a result, the oxidation system becomes homogeneous.