

## ORGANIC CHEMISTRY | RESEARCH ARTICLE

# Mild oxidative aromatization of 1,4-dihydropyridines with trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxalane promoted by ammonium bromide/HOAc in water/MeCN

Kaveh Khosravi

*Cogent Chemistry* (2015), 1: 1052615



Received: 05 March 2015  
Accepted: 14 May 2015  
Published: 09 June 2015

\*Corresponding author: Kaveh Khosravi,  
Faculty of Science, Department of  
Chemistry, Arak University, Arak 38156-  
8-8349, Iran  
E-mails: [khosravi.kaveh@gmail.com](mailto:khosravi.kaveh@gmail.com);  
[k-khosravi@araku.ac.ir](mailto:k-khosravi@araku.ac.ir)

Reviewing editor:  
George Weaver, University of  
Loughborough, UK

Additional information is available at  
the end of the article

## ORGANIC CHEMISTRY | RESEARCH ARTICLE

# Mild oxidative aromatization of 1,4-dihydropyridines with trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane promoted by ammonium bromide/HOAc in water/MeCN

Kaveh Khosravi<sup>1\*</sup>

**Abstract:** Trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane (DHPDMDO)/NH<sub>4</sub>Br/HOAc has been used as a new and effective oxidant for oxidative aromatization of 1,4-dihydropyridines to the corresponding pyridines in the presence of a catalytic amount of acetic acid at room temperature in water/MeCN in good yields within short times.

**Subjects:** Chemistry; Medicinal & Pharmaceutical Chemistry; Organic Chemistry

**Keywords:** Trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane; 1,4-dihydropyridines; NH<sub>4</sub>Br; pyridines; oxidative aromatization

### 1. Introduction

1,4-dihydropyridines (1,4-DHPs) have been of interest because of their biological and medicinal activities such as calcium antagonists (Peri, Padmanabhan, Rutledge, Singh, & Triggle, 2000; Visentin et al., 2004; Zamponi et al., 2003; Zarghi, Sadeghi, Fassihi, Faizi, & Shafiee, 2003), anti-tubercular agents (Kharkar et al., 2002), anti-tumor (Tsuruo, Iida, Nojiri, Tsukagoshi, & Sakurai, 1983), bronchodilating (Chapman, Danko, & Siegels, 1984), and antiviral activities (Krauze et al., 1999). Aromatization of 1,4-DHPs has attracted considerable attention as they provide easy access to pyridine derivatives, which show anti-hypoxic and anti-ischemic activities (Hashemi, Ahmadibeni, & Ghafuri, 2003; Khadilkar & Borkar, 1998; Litvić et al., 2005; Maquestiau, Mayence, & Eynde, 1991; Mashraqui & Karnik, 1998; Nakamichi, Kawashita, & Hayashi, 2002; Pfister, 1990; Sabitha, Kiran Kumar Ready, Srinivas, Fatima, & Yadav, 2003; Sausins & Duburs, 1988; Vanden Eynde, Delfosse, Mayence, & Van Haverbeke, 1995; Vanden Eynde, Mayence, & Maquestiau, 1992; Varma & Kumar, 1999). Various oxidants have been used for the aromatization of 1,4-DHPs (Hashemi et al., 2003; Litvić et al., 2005; Maquestiau et al., 1991;



Kaveh Khosravi

### ABOUT THE AUTHOR

Kaveh Khosravi obtained his PhD in organic chemistry in 2011 from Bu Ali Sina University, Hamedan, Iran. His doctoral thesis was on synthesis of gem-dihydroperoxides and their application in organic chemistry. He worked as an assistant professor at Arak University in 2012 until now. His current research interest focuses on synthesis and characterization of gem-dihydroperoxides and their application in the synthesis of organic compounds.

In this work, trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane has been used as a powerful peroxidic oxidant for efficient aromatization of 1,4-dihydropyridines.

### PUBLIC INTEREST STATEMENT

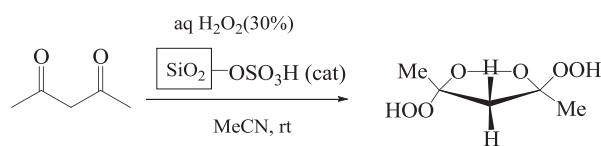
Gem-dihydroperoxides as organic compounds are good oxidizing reagent that have been used for oxidation of organic reaction of late. As regards the importance of oxidative aromatization in organic chemistry, I am interested in the application of gem-dihydroperoxides and especially trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane (DHPDMDO) as an effective and powerful oxidant in organic synthesis. In this work, as regards the importance of pyridines in medicinal chemistry, DHPDMDO has been used for aromatization of 1,4-dihydropyridines under mild conditions.

Mashraqui & Karnik, 1998; Nakamichi et al., 2002; Pfister, 1990; Sabitha et al., 2003; Sausins & Duburs, 1988; Vanden Eynde et al., 1995; Vanden Eynde et al., 1992; Varma & Kumar, 1999); however, unfortunately, most of these methods use strong oxidants accomplished by the transition metals such as ferric nitrate (Khadilkar & Borkar, 1998),  $\text{CrO}_3$  (Sausins & Duburs, 1988),  $\text{MnO}_2$  (Vanden Eynde et al., 1995), PCC (Vanden Eynde et al., 1992),  $\text{Zr}(\text{NO}_3)_4$  (Sabitha et al., 2003),  $\text{Bi}(\text{NO}_3)_3$  (Mashraqui & Karnik, 1998), clay-supported cupric nitrate (Maquestiau et al., 1991),  $\text{H}_2\text{O}_2/\text{Co}(\text{OAc})_2$  (Hashemi et al., 2003),  $\text{Pb}(\text{OAc})_4$  (Litvić et al., 2005),  $\text{RuCl}_3/\text{O}_2$  (Sausins & Duburs, 1988), ceric ammonium nitrate (CAN) (Pfister, 1990), Pd/C (Nakamichi et al., 2002),  $\text{KMnO}_4$  (Eynde, D'Orazio, & Haverbeke, 1994) and  $\text{Mn}(\text{OAc})_3$  (Varma & Kumar, 1999). Also, some other oxidants such as DDQ (Vanden Eynde et al., 1995), heteropolyacid/ $\text{NaNO}_2/\text{SiO}_2$  (Niknam, Zolfigol, Razavian, & Mohammadpoor, 2005),  $\text{I}_2/\text{MeOH}$  (Yadav, Subba Reddy, Sabitha, & Kiran Kumar Reddy, 2000), nitric oxide (Itoh, Nagata, Okada, & Ohsawa, 1995),  $\text{HNO}_3$  (García, Delgado, Cano, & Alvarez, 1993) and  $\text{SeO}_2$  (Cai, Yang, & Zhang, 2005) have been used for aromatization of 1,4-dihydropyridines. But, many of these methodologies suffer from drawbacks such as requiring intensive reaction conditions or needing excess oxidants or long times and afford only poor to moderate yields of products with difficult work-up procedure (Cai et al., 2005; Garcia et al., 1993; Hashemi et al., 2003; Itoh et al., 1995; Litvić et al., 2005; Maquestiau et al., 1991; Mashraqui & Karnik, 1998; Nakamichi et al., 2002; Niknam et al., 2005; Pfister, 1990; Sabitha et al., 2003; Sausins & Duburs, 1988; Eynde et al., 1994; Vanden Eynde et al., 1995; Vanden Eynde et al., 1992; Varma & Kumar, 1999; Yadav et al., 2000). In addition, many of these reported procedures for oxidative aromatization are also associated with side reactions and generate by-products. Thus, as regards the importance of pyridines, the development of a simple, efficient, mild, and versatile method for the oxidation of 1,4-DHP is of interest in organic methodology. Recently, gem-dihydroperoxides have been synthesized and have been used for oxidation reactions (Bunge, Hamann, & Liebscher, 2009; Bunge, Hamann, McCalmont, & Liebscher, 2009; Das, Krishnaiah, Veeranjanyulu, & Ravikanth, 2007; Das, Veeranjanyulu, Krishnaiah, & Balasubramanyam, 2008; Ghorai & Dussault, 2008; Li, Hao, Zhang, & Wu, 2009; Žmitek, Zupan, Stavber, & Iskra, 2006; Žmitek, Zupan, Stavber, & Iskra, 2007). We have synthesized trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxalane (Scheme 1) and used it as a powerful oxidant in some organic reactions (Azarifar & Khosravi, 2010a; Azarifar & Khosravi, 2010b; Azarifar, Khosravi, & Soleimane, 2009; Azarifar, Najminejad, & Khosravi, 2013; Khosravi, 2014; Khosravi, 2015; Khosravi & Kazemi, 2012; Khosravi, Mobinikhaledi, Kazemi, Azarifar, & Rahmani, 2014; Khosravi, Pirbodaghi, Kazemi, & Asghari, 2015). So, in continuation of our interest in the application of DHPDMDOs, we used DHPDMDOs for *in situ* generation of  $\text{Br}^+$  from  $\text{NH}_4\text{Br}$  for catalysis of oxidative aromatization of 1,4-dihydropyridines to corresponding pyridines under mild conditions and short reaction times (Scheme 2).

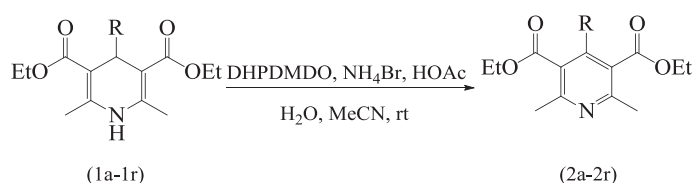
## 2. Experimental

CAUTION: Although we did not encounter any problem with DHPDMDO, similar to all peroxides, it is potentially explosive and should be handled with precautions; all reactions should be carried out behind a safety shield inside a fume hood and transition metal salts or heating should be avoided.

**Scheme 1. Synthesis of trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxalane (DHPDMDO).**



**Scheme 2. Oxidative aromatization of 1,4-dihydropyridines.**



### 2.1. Preparation of trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxalane (DHPDMDO)

To a stirred solution of acetylacetone (0.1 mL, 1 mmol) in CH<sub>3</sub>CN (4 mL), SSA (100 mg) was added and stirring of the reaction mixture was continued for 5 min at room temperature. Then, aqueous 30% H<sub>2</sub>O<sub>2</sub> (5 mmol) was added to the reaction mixture and was stirred for 30 min at room temperature. After completion of the reaction as monitored by TLC, the resulting mixture was filtered and washed with EtOAc (2 × 5 mL) to separate the solid catalyst. The combined filtrates were diluted with water (5 mL) and extracted with EtOAc (3 × 5 mL). The organic layer was separated, dried over anhydrous MgSO<sub>4</sub>, and evaporated under reduced pressure to give almost pure white crystalline product 1 (Scheme 1). Trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxalane has been characterized by elemental analysis, IR, <sup>1</sup>H NMR, and <sup>13</sup>C NMR spectroscopies. Also, the amount of peroxide is determined by iodometric titration.

### 2.2. General experimental procedure for oxidative aromatization of 1,4-dihydropyridines (DHPs)

A mixture of 1,4-DHPs (1 mmol), NH<sub>4</sub>Br (0.1 mmol, 0.01 g), acetic acid (0.1 mmol, 0.006 mL) in water (3 mL) and MeCN (2 mL) is prepared. Then, DHPDND (0.05 g, 0.3 mmol) was added to this mixture and stirred for an appropriate time at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, Na<sub>2</sub>SO<sub>3</sub> 1 M (1 mL) was added and stirred for 10 min. Then, water (15 mL) was added. The products were extracted by EtOAc, dried with MgSO<sub>4</sub>, and evaporated for obtaining pure products.

### 2.3. Spectroscopic data of DHPDMDO

White crystal, Mp: 98–100°C; IR (KBr): 3441 (br), 1618, 1456, 1155 cm<sup>-1</sup>; <sup>1</sup>H NMR (90 MHz, CDCl<sub>3</sub>) δ: 1.60 (s, 6H, Me), 2.67 (s, 2H, CH<sub>2</sub>), 8.45 (4H, br, peroxide Hydrogen). <sup>13</sup>C NMR: (22.5 MHz, D<sub>2</sub>O) δ: 16.50, 50.63, 112.00. Elemental Analysis: Calculated: C, 36.15; H, 6.07; Found: C: 37.02; H: 6.25.

## 3. Results and discussion

As regards the importance of *gem*-dihydroperoxides, trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxalane (DHPDMDO) has been synthesized and used as a new, solid, and powerful oxidant in organic synthesis by our research group (Anniyappan et al., 2002; Dehghanpour, Heravi, & Derikvand, 2007; Fang, Liu, & Li, 2007; Filipan-Litvić, Litvić, & Vinkinić, 2008a; Filipan-Litvić, Litvić, & Vinkinić, 2008b; Gorjizadeh & Abdollahi-Alibeik, 2011; Heravi, Behbahani, Oskooie, & Shoar, 2005; Heravi et al., 2009; Karade, Gampawar, Kondre, & Shinde, 2008; Ko & Kim, 1999; Mao, Jin, Liu, & Wu, 2000; Mashraqui & Karnik, 1998; Zolfigol et al., 2005; Zeynizadeh, Dilmaghani, & Mirzaei, 2007). DHPDMDO is prepared easily from acetyl acetone and aqueous hydrogen peroxide in the presence of silica sulfuric acid (SSA) (Anniyappan et al., 2002) (Scheme 1). In this work, we wish to report for the first time an efficient and simple procedure for the oxidative aromatization of 1,4-dihydropyridines to the corresponding pyridines, using the trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxalane/NH<sub>4</sub>Br/HOAc system in water/MeCN at room temperature (Scheme 2).

At first, the condition of the reaction (solvent, amount of oxidant and NH<sub>4</sub>Br) is studied and in terms of yield and reaction time, water/MeCN is selected as the best solvent and amounts of oxidant and NH<sub>4</sub>Br are optimized (Table 1). It is notable that the addition of HOAc improved yields and reduced reaction times.

As summarized in Table 2, various 1,4-DHPs substituted by both aliphatic and aromatic groups were oxidized to corresponding pyridines in excellent yields and short reaction times. The aromatic substituents with both electron-withdrawing (Table 2, entries 8–14) and electron-donating groups (Table 2, entries 1–6, 15–17) were oxidized. From the obtained results, it seems that the electron-releasing groups accelerate the reaction. Also, 1,4-DHP containing the furyl substitution as a heterocyclic substitution has been successfully aromatized (Table 2, entry 18).

The suggested mechanism shown in Scheme 3 describes the *in situ* generation of Br<sup>•</sup>. As the HOAc converts BrOH to more active BrOAc, the addition of a catalytic amount of HOAc clearly decreases

**Table 1. Optimization of reaction conditions for oxidation of diethyl 1,4-dihydro-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (1 mmol)**

Entry	DHPDMDO (mmol)	NH <sub>4</sub> Br (mmol)	HOAc (mmol)	Solvent <sup>a</sup>	Time (min)	Yield (%)
1	0.3	0.05	–	MeCN	60	50
2	0.3	0.1	–	MeCN	30	80
3	0.3	0.2	–	MeCN	25	81
4	0.3	0.5	–	MeCN	25	70
5	0.3	0.8	–	MeCN	20	40
6	0.3	0.1	0.05	MeCN	25	90
7	0.3	0.1	0.05	CHCl <sub>3</sub>	60	70
8	0.3	0.1	0.05	CCl <sub>4</sub>	45	85
9	0.3	0.1	0.05	THF	30	90
10	0.3	0.1	0.05	H <sub>2</sub> O/MeCN	21	95
11	0.1	0.1	0.05	H <sub>2</sub> O/MeCN	45	87
12	0.2	0.1	0.05	H <sub>2</sub> O/MeCN	35	90
13	0.5	0.1	0.05	H <sub>2</sub> O/MeCN	20	85
14	1	0.1	0.05	H <sub>2</sub> O/MeCN	18	75

<sup>a</sup>Solvent in all entries is 5 mL, for entries 10–14: H<sub>2</sub>O (3 mL) and MeCN (2 mL).

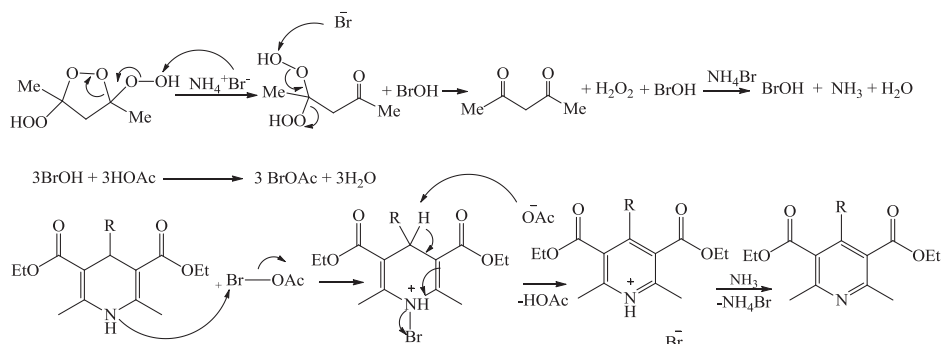
**Table 2. Oxidative aromatization of 1,4-dihydropyridines to the corresponding pyridines by DHPDMDO/NH<sub>4</sub>Br/HOAc system in water/MeCN at r.t.<sup>a</sup>**

Entry	Compound	R	Time (min)	Yield (%) <sup>b</sup>	Mp (°C)	
					Found	Reported
1	2a	H	12	96	67–69	68–70 (Heravi et al., 2007)
2	2b	CH <sub>3</sub>	14	94	Oil	Oil (Heravi et al., 2007)
3	2c	CH <sub>3</sub> CH <sub>2</sub>	17	95	Oil	Oil (Heravi et al., 2007)
4	2d	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub>	17	95	Oil	Oil (Chen and Zhang, 2007)
5	2e	Isopropyl-	17	93	72–74	70–72 (Heravi et al., 2007)
6	2f	C <sub>6</sub> H <sub>5</sub> CH=CH	18	97	Oil	Oil (Zeynizadeh et al., 2007)
7	2g	C <sub>6</sub> H <sub>5</sub>	21	95	61–63	60–62 (Heravi et al., 2007)
8	2h	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	30	95	114–116	113–114 (Chen & Zhang, 2007)
9	2i	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	27	94	60–62	62–63 (Heravi et al., 2007)
10	2j	2-Cl-C <sub>6</sub> H <sub>4</sub>	30	96	72–74	70–71 (Zeynizadeh et al., 2007)
11	2k	4-Cl-C <sub>6</sub> H <sub>4</sub>	27	98	61–63	64–66 (Heravi et al., 2007)
12	2l	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	32	95	76–78	78–79 (Zeynizadeh et al., 2007)
13	2m	3-Br-C <sub>6</sub> H <sub>4</sub>	31	93	72–74	70–72 (Zeynizadeh et al., 2007)
14	2n	4-F-C <sub>6</sub> H <sub>4</sub>	35	97	92–94	90–92 (Liao, Lin, Lu, & Wang, 2010)
15	2o	4-MeO-C <sub>6</sub> H <sub>4</sub>	26	94	50–52	49–50 (Zeynizadeh et al., 2007)
16	2p	4-Me-C <sub>6</sub> H <sub>4</sub>	25	99	72–74	72–73 (Heravi et al., 2007)
17	2q	4-HO-C <sub>6</sub> H <sub>4</sub>	20	93	170–172	172–173 (Liao et al., 2010)
18	2r	2-Furyl	31	92	Oil	Oil (Liao et al., 2010)

<sup>a</sup>Conditions: 1,4-DHPs (1 mmol), NH<sub>4</sub>Br (0.1 mmol, 0.01 g), acetic acid (0.1 mmol, 0.006 mL), DHPDMDO (0.05 g, 0.3 mmol), water (3 mL) and MeCN (2 mL), r.t. The structures of the products were established from their physical properties and spectral (<sup>1</sup>H NMR, <sup>13</sup>C NMR, and IR) analysis and compared with the data reported in the literature.

<sup>b</sup>Isolated yield.

**Scheme 3. Suggested mechanism for oxidative aromatization of 1,4-dihydropyridines.**



**Table 3. Comparing the present method with some other previously reported procedures for compound 2g**

Entry	Oxidant	Conditions <sup>a</sup>	Solvent	Time (h)	Yield (%)	Reference
1	DHPDMDO/ $\text{NH}_4\text{Br}$ /HOAc	r.t	$\text{H}_2\text{O}/\text{MeCN}$	0.35	95	This method
2	$\text{Fe}(\text{ClO}_4)_3$	r.t	acetic acid	1.5	93	Heravi et al. (2005)
3	Urea nitrate	Reflux	MeCN	2	91 (by product)	Anniyappan et al. (2002)
4	4-Phenyl-1,2,4-triazole-3,5-dione	r.t	$\text{CH}_2\text{Cl}_2$	0.42	88	Zolfigol et al. (2005)
5	Magtrieve TM ( $\text{CrO}_2$ )	Reflux	$\text{CHCl}_3$	2	97	Ko and Kim (1999)
6	9-Phenyl-10-methylacridinium	REFLUX, hv	MeCN	12	96	Fang et al. (2007)
7	Dess-Martin periodinane/ $\text{KBr}$	r.t	MeCN	3	82	Karade et al. (2008)
8	$\text{UHP}/\text{I}_2$	r.t	AcOEt	12	89	Filipan-Litvić et al. (2008a)
9	Bismuth Nitrate Pentahydrate	r.t	AcOH	7	90	Mashraqui and Karnik (1998)
10	$\text{Ag}_2\text{O}$	Reflux	MeCN	1.7	96	Zeynizadeh et al. (2007)
11	$\text{Cu}(\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_2)$	Reflux	AcOH	1	90	Dehghanpour et al. (2007)
12	n-Butyltriphenylphosphonium peroxodisulfate	Reflux	MeCN	0.25	87	Gorjizadeh and Abdollahi-Alibeik (2011)
13	$\text{Pd}/\text{C}$	80 C	AcOH	2	97	Nakamichi et al. (2002)
14	$\text{Mn}(\text{pbdo})_2\text{Cl}_2/\text{Al-MCM-41}$	Reflux	AcOH	2	89	Heravi et al. (2009)
15	$\text{H}_6\text{PMo}_9\text{V}_3\text{O}_{40}$	Reflux	AcOH	1.1	96	Heravi et al. (2007)
16	S-Nitrosoglutathione	r.t	$\text{MeCN}/\text{H}_2\text{O}$	10	70	Mao et al. (2000)
17	$\text{VOCl}_3$	r.t	$\text{CH}_2\text{Cl}_2$	1	97	Filipan-Litvić et al. (2008b)

<sup>a</sup>r.t stands for room temperature.

reaction times. The *in situ* generated  $\text{Br}^+$  activates the nitrogen of the ring as an efficient Lewis acid. Then, the acetate anion as a base removes the  $\text{H}^+$  and finally the heterocyclic ring has been aromatized.



In many of the previously reported methodologies, transition metals have been used as catalysts that are toxic, expensive, and pollutants of environment. Also, the solvents of these methodologies are toxic. In addition, in most of these methodologies, by-products are observed when the DHP ring has an alkyl substitution. We wish to eliminate these defects using the DHPDMDO/ $\text{NH}_4\text{Br}$ /HOAc system in water/MeCN as a solvent. The obtained data for diethyl 1,4-dihydro-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (Table 2, entry 5) by this method are compared with other reported data in Table 3. As shown in Table 3, the obtained yield and the reaction time are notable in comparison with other reported methods.

Finally, although the elimination of 4-substitution (R) and the formation of by-product have been observed in many other reported oxidation reaction, it is very notable that no by product was observed via this method.

#### 4. Conclusion

In summary, DHPDMDO has been conveniently used as an effective and high oxygen-content oxidant for the oxidation of various substituted 1,4-dihydropyridines to corresponding pyridines. The reactions proceed under mild conditions at room temperature to afford the corresponding products in quantitative yields. This protocol may be considered as environmentally benign since no extra toxic catalyst has been used in this method. Also, no by-product has been observed.

#### Funding

Kaveh Khosravi would like to thank Arak University for financial support to this work.

#### Author details

Kaveh Khosravi<sup>1</sup>

E-mails: [khosravi.kaveh@gmail.com](mailto:khosravi.kaveh@gmail.com); [k-khosravi@araku.ac.ir](mailto:k-khosravi@araku.ac.ir)

<sup>1</sup> Faculty of Science, Department of Chemistry, Arak University, Arak 38156-8-8349, Iran.

#### Citation information

Cite this article as: Mild oxidative aromatization of 1,4-dihydropyridines with trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane promoted by ammonium bromide/HOAc in water/MeCN, Kaveh Khosravi, *Cogent Chemistry* (2015), 1: 1052615.

#### Cover image

Source: Author.

#### References

- Anniyappan, M., Muralidharan, D., & Perumal, P. T. (2002). A novel application of the oxidizing properties of urea nitrate and peroxydisulfate-cobalt(II): Aromatization of NAD(P)H model Hantzsch 1,4-dihydropyridines. *Tetrahedron*, 58, 5069–5073. [http://dx.doi.org/10.1016/S0040-4020\(02\)00461-1](http://dx.doi.org/10.1016/S0040-4020(02)00461-1)
- Azarifar, D., & Khosravi, K. (2010a). Facile epoxidation of  $\alpha,\beta$ -unsaturated ketones with trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane as an efficient oxidant. *Synlett*, 18, 2755–2758. <http://dx.doi.org/10.1055/s-0030-1258996>
- Azarifar, D., & Khosravi, K. (2010b). Trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane as a novel and efficient reagent for selective sulfoxidation of sulfides under catalyst-free condition. *European Journal of Chemistry*, 1, 15–19. <http://dx.doi.org/10.5155/eurjchem.1.1.15-19.6>
- Azarifar, D., Khosravi, K., & Soleimane, F. (2009). Stannous chloride dihydrate: A novel and efficient catalyst for the synthesis of gem-dihydroperoxides from ketones and aldehydes. *Synthesis*, 2009, 2553–2556. <http://dx.doi.org/10.1055/s-0029-1217394>
- Azarifar, D., Najminejad, Z., & Khosravi, K. (2013). Synthesis of gem-dihydroperoxides from ketones and aldehydes using silica sulfuric acid as heterogeneous reusable catalyst. *Synthetic Communications*, 43, 826–836. <http://dx.doi.org/10.1080/00397911.2011.610549>
- Bunge, A., Hamann, H. J., & Liebscher, J. (2009). A simple, efficient, and versatile synthesis of primary gem-dihydroperoxides from aldehydes and hydrogen peroxide. *Tetrahedron Letters*, 50, 524–526. <http://dx.doi.org/10.1016/j.tetlet.2008.11.055>
- Bunge, A., Hamann, H.-J., McCalmont, E., & Liebscher, J. (2009). Enantioselective epoxidation of 2-substituted 1,4-naphthoquinones using gem-dihydroperoxides. *Tetrahedron Letters*, 50, 4629–4632. <http://dx.doi.org/10.1016/j.tetlet.2009.05.096>
- Cai, X., Yang, H., & Zhang, G. (2005). Aromatization of 1,4-dihydropyridines with selenium dioxide. *Canadian Journal of Chemistry*, 83, 273–275. <http://dx.doi.org/10.1139/v05-058>
- Chapman, R. W., Danko, G., & Siegels, M. I. (1984). Effect of extra- and intracellular calcium blockers on histamine and antigen-induced bronchospasms in guinea pigs and rats. *Pharmacology*, 29, 282–291.
- Chen, Z. Y., & Zhang, W. (2007). Oxidative aromatization of Hantzsch 1,4-dihydropyridines by aqueous hydrogen peroxide-acetic acid. *Chinese Chemical Letters*, 18, 1443–1446. <http://dx.doi.org/10.1016/j.ccllet.2007.10.010>
- Das, B., Krishnaiah, M., Veeranjanyulu, B., & Ravikanth, B. (2007). A simple and efficient synthesis of gem-dihydroperoxides from ketones using aqueous hydrogen peroxide and catalytic ceric ammonium nitrate. *Tetrahedron Letters*, 48, 6286–6289. <http://dx.doi.org/10.1016/j.tetlet.2007.07.012>
- Das, B., Veeranjanyulu, B., Krishnaiah, M., & Balasubramanyam, P. (2008). Synthesis of gem-dihydroperoxides from ketones using silica-supported sodium hydrogen sulfate as a heterogeneous catalyst. *Journal of Molecular Catalysis A: Chemical*, 284, 116–119. <http://dx.doi.org/10.1016/j.molcata.2008.01.016>
- Dehghanpour, S., Heravi, M. M., & Derikvand, F. (2007).  $\text{N,N}'$ -ethylene-bis(benzoylacetoniminato) Copper (II),  $\text{Cu}(\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_2)$ , a new reagent for aromatization of Hantzsch 1,4-dihydropyridines. *Molecules*, 12, 433–438. <http://dx.doi.org/10.3390/12030433>
- Eynde, J. J. V., D'Orazio, R., & Van Haverbeke, Y. (1994). Potassium permanganate, a versatile reagent for

- the aromatization of Hantzsch 1,4-dihydropyridines. *Tetrahedron*, 50, 2479–2484.  
[http://dx.doi.org/10.1016/S0040-4020\(01\)86964-7](http://dx.doi.org/10.1016/S0040-4020(01)86964-7)
- Fang, X., Liu, Y.-C., & Li, C. (2007). 9-Phenyl-10-methylacridinium: A highly efficient and reusable organocatalyst for mild aromatization of 1,4-Dihydropyridines by molecular oxygen. *The Journal of Organic Chemistry*, 72, 8608–8610.  
<http://dx.doi.org/10.1021/jo701796n>
- Filipan-Litvić, M., Litvić, M., & Vinković, V. (2008a). An efficient, metal-free, room temperature aromatization of Hantzsch-1,4-dihydropyridines with urea-hydrogen peroxide adduct, catalyzed by molecular iodine. *Tetrahedron*, 64, 5649–5656. <http://dx.doi.org/10.1016/j.tet.2008.04.040>
- Filipan-Litvić, M., Litvić, M., & Vinković, V. (2008b). Rapid, efficient, room temperature aromatization of Hantzsch-1,4-dihydropyridines with vanadium(V) salts: Superiority of classical technique versus microwave promoted reaction. *Tetrahedron*, 64, 10912–10918.  
<http://dx.doi.org/10.1016/j.tet.2008.08.103>
- García, O., Delgado, F., Cano, A. C., & Alvarez, C. (1993). Oxydation d'esters de Hantzsch, par le nouveau système HNO<sub>2</sub>/bentonite, et irradiation aux micro-ondes [Hantzsch esters oxidation by the new HNO<sub>2</sub>/bentonite system, and irradiation with microwaves]. *Tetrahedron Letters*, 34, 623–625.  
[http://dx.doi.org/10.1016/S0040-4039\(00\)61635-0](http://dx.doi.org/10.1016/S0040-4039(00)61635-0)
- Ghorai, P., & Dussault, P. H. (2008). Mild and efficient Re(VII)-catalyzed synthesis of 1,1-dihydroperoxides. *Organic Letters*, 10, 4577–4579.  
<http://dx.doi.org/10.1021/ol801859c>
- Gorjizadeh, M., & Abdollahi-Alibeik, M. (2011). n-Butyltriphenylphosphonium peroxodisulfate: A cheap and efficient reagent for the aromatization of Hantzsch 1,4-dihydropyridines. *Chinese Chemical Letters*, 22, 61–64.  
<http://dx.doi.org/10.1016/j.ccl.2010.07.022>
- Hashemi, M. M., Ahmadibeni, Y., & Ghafari, H. (2003). Aromatization of Hantzsch 1,4-dihydropyridines by hydrogen peroxide in the presence of cobalt(II) acetate. *Monatshefte für Chemie/Chemical Monthly*, 134, 107–110.
- Heravi, M. M., Behbahani, F. K., Oskooie, H. A., & Shoar, R. H. (2005). Catalytic aromatization of Hantzsch 1,4-dihydropyridines by ferric perchlorate in acetic acid. *Tetrahedron Letters*, 46, 2775–2777.  
<http://dx.doi.org/10.1016/j.tetlet.2005.02.147>
- Heravi, M. M., Derikvand, F., Hassan-Pour, S., Bakhtiari, K., Bamoharram, F. F., & Oskooie, H. A. (2007). Oxidative aromatization of Hantzsch 1,4-dihydropyridines in the presence of mixed-addenda vanadomolybdophosphate heteropolyacid, H<sub>8</sub>PMo<sub>9</sub>V<sub>3</sub>O<sub>40</sub>. *Bioorganic & Medicinal Chemistry Letters*, 17, 3305–3309.
- Heravi, M. M., Oskooie, H. A., Malakooti, R., Alimadadi, B., Alinejad, H., & Behbahani, F. K. (2009). Oxidative aromatization of Hantzsch 1,4-dihydropyridines in the presence of a catalytic amount of Mn(pbdo)<sub>2</sub>Cl<sub>2</sub>/MCM-41 or Mn(pbdo)<sub>2</sub>Cl<sub>2</sub>/Al-MCM-41 as reusable and green catalysts. *Catalysis Communications*, 10, 819–822.  
<http://dx.doi.org/10.1016/j.catcom.2008.12.005>
- Itoh, T., Nagata, K., Okada, M., & Ohsawa, A. (1995). The aromatization of Hantzsch dihydropyridines with nitric oxide (NO). *Tetrahedron Letters*, 36, 2269–2272.  
[http://dx.doi.org/10.1016/0040-4039\(95\)00268-H](http://dx.doi.org/10.1016/0040-4039(95)00268-H)
- Karade, N. N., Gampawar, S. V., Kondre, J. M., & Shinde, S. V. (2008). An efficient combination of Dess-Martin periodinane with molecular iodine and KBr for the facile oxidative aromatization of Hantzsch 1,4-dihydropyridines. *Arkivoc*, xii, 9–16. <http://dx.doi.org/10.3998/ark.5550190.0009.c02>
- Khadilkar, B., & Borkar, S. (1998). Silica gel supported ferric nitrate: A convenient oxidizing reagent. *Synthetic Communications*, 28, 207–212.  
<http://dx.doi.org/10.1080/00397919808005712>
- Kharkar, P. S., Desai, B., Gaveria, H., Varu, B., Loria, R., Naliapara, Y., ... Kulkarni, V. M. (2002). Three-dimensional quantitative structure–activity relationship of 1,4-dihydropyridines as antitubercular agents. *Journal of Medicinal Chemistry*, 45, 4858–4867.  
<http://dx.doi.org/10.1021/jm020217z>
- Khosravi, K. (2014). Mild and efficient oxidation of 2-pyrazolines and isoxazolines by trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane-NH<sub>4</sub>Cl-HOAc in water–MeCN. *Research on Chemical Intermediates*. doi:10.1007/s11164-014-1626-5
- Khosravi, K. (2015). Cesium nitrate: As an efficient catalyst for synthesis of gem-dihydroperoxides from aldehydes and ketones using aqueous 30% H<sub>2</sub>O<sub>2</sub>. *Cogent Chemistry*, 1, 1–9. <http://dx.doi.org/10.1080/23312009.2014.1002339>
- Khosravi, K., & Kazemi, S. (2012). Green, mild and efficient bromination of aromatic compounds by HBr promoted by trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane in water as a solvent. *Chinese Chemical Letters*, 23, 387–390.  
<http://dx.doi.org/10.1016/j.ccl.2012.01.009>
- Khosravi, K., Mobinikhaledi, A., Kazemi, S., Azarifar, D., & Rahmani, P. (2014). Trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane/HOAc/KI system as a new and mild catalyst for efficient synthesis of 1-H-benzimidazoles and 1-H-benzothiazoles in water. *Iranian Journal of Catalysis*, 4, 25–31.
- Khosravi, K., Pirbodaghi, F., Kazemi, S., & Asghari, A. (2015). Sulfamic acid: As a green and reusable homogeneous catalyst for peroxidation of ketones and aldehydes using aqueous 30% H<sub>2</sub>O<sub>2</sub>. *Journal of the Iranian Chemical Society*. doi:10.1007/s13738-015-0598-8
- Ko, K.-Y., & Kim, J.-Y. (1999). Aromatization of Hantzsch 1,4-dihydropyridines with Magtrieve™. *Tetrahedron Letters*, 40, 3207–3208.  
[http://dx.doi.org/10.1016/S0040-4039\(99\)00467-0](http://dx.doi.org/10.1016/S0040-4039(99)00467-0)
- Krauze, A., Gërmane, S., Eberlin JnE Š, O., Šturms, I., Klusá, V., & Duburs, G. (1999). Derivatives of 3-cyano-6-phenyl-4-(3'-pyridyl)-pyridine-2(1H)-thione and their neurotropic activity. *European Journal of Medicinal Chemistry*, 34, 301–310. [http://dx.doi.org/10.1016/S0223-5234\(99\)80081-6](http://dx.doi.org/10.1016/S0223-5234(99)80081-6)
- Li, Y., Hao, H.-D., Zhang, Q., & Wu, Y. (2009). A broadly applicable mild method for the synthesis of gem-diperoxides from corresponding ketones or 1,3-dioxolanes. *Organic Letters*, 11, 1615–1618.  
<http://dx.doi.org/10.1021/ol900262t>
- Liao, X., Lin, W., Lu, J., & Wang, C. (2010). Oxidative aromatization of Hantzsch 1,4-dihydropyridines by sodium chlorite. *Tetrahedron Letters*, 51, 3859–3861.  
<http://dx.doi.org/10.1016/j.tetlet.2010.05.091>
- Litvić, M., Cepanec, I., Filipan, M., Kos, K., Bartolinčić, A., Drušković, V., ... Vinković, V. (2005). Mild, selective and high-yield oxidation of Hantzsch 1,4-dihydropyridines with lead (IV) acetate. *Heterocycles*, 65, 23–35.  
<http://dx.doi.org/10.3987/COM-04-10194>
- Mao, Y. -Zh., Jin, M. -Zh., Liu, Zh. -L., & Wu, L. M. (2000). Oxidative reactivity of S-nitrosoglutathione with Hantzsch 1,4-dihydropyridine. *Organic Letters*, 2, 741–742.  
<http://dx.doi.org/10.1021/ol990367c>
- Maquestiau, A., Mayence, A., & Eynde, J. J. V. (1991). Ultrasound-promoted aromatization of Hantzsch 1,4-dihydropyridines by clay-supported cupric nitrate. *Tetrahedron Letters*, 32, 3839–3840.  
[http://dx.doi.org/10.1016/S0040-4039\(00\)79390-7](http://dx.doi.org/10.1016/S0040-4039(00)79390-7)
- Mashraqui, S. H., & Karnik, M. A. (1998). Bismuth nitrate pentahydrate: A convenient reagent for the oxidation of Hantzsch 1,4-dihydropyridines. *Synthesis*, 5, 713–714.  
<http://dx.doi.org/10.1055/s-1998-4516>



- Nakamichi, N., Kawashita, Y., & Hayashi, M. (2002). Oxidative aromatization of 1,3,5-trisubstituted pyrazolines and Hantzsch 1,4-dihydropyridines by Pd/C in acetic acid. *Organic Letters*, 4, 3955–3957. <http://dx.doi.org/10.1021/ol0268135>
- Niknam, K., Zolfigol, M. A., Razavian, S. M., & Mohammadpoor, B. I. (2005). Molybdato-phosphoric acid/NaNO<sub>2</sub>/wet SiO<sub>2</sub> as an efficient system for oxidation of 1,4-dihydropyridines under mild and heterogeneous conditions. *Heterocycles*, 65, 657–660. <http://dx.doi.org/10.3987/COM-04-10302>
- Peri, R., Padmanabhan, S., Rutledge, A., Singh, S., & Triggler, D. J. (2000). Permanently charged chiral 1,4-dihydropyridines: Molecular probes of L-type calcium channels. Synthesis and pharmacological characterization of methyl ( $\omega$ -trimethylalkylammonium) 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate iodide, calcium channel antagonists. *Journal of Medicinal Chemistry*, 43, 2906–2914. <http://dx.doi.org/10.1021/jm000028l>
- Pfister, J. R. (1990). Rapid, high-yield oxidation of Hantzsch-type 1,4-dihydropyridines with ceric ammonium nitrate. *Synthesis*, 8, 689–690. <http://dx.doi.org/10.1055/s-1990-26982>
- Sabitha, G. G., Kiran Kumar Ready, G. S. K., Srinivas, C., Fatima, N., & Yadav, J. S. (2003). Zr(NO<sub>3</sub>)<sub>4</sub>: A versatile oxidizing agent for aromatization of Hantzsch 1,4-dihydropyridines and 1,3,5-trisubstituted pyrazolines. *Synthesis*, 8, 1267–1271.
- Sausins, A., & Duburs, G. (1988). Reactions of 1,4-dihydropyridines. *Heterocycles*, 27, 291–314.
- Tsuruo, T., Iida, H., Nojiri, M., Tsukagoshi, S., & Sakurai, Y. (1983). Circumvention of vincristine and adriamycin resistance *in vitro* and *in vivo* by calcium influx blockers. *Cancer Research*, 43, 2905–2910.
- Vanden Eynde, J. J., Delfosse, F., Mayence, A., & Van Haverbeke, Y. (1995). Old reagents, new results: Aromatization of Hantzsch 1,4-dihydropyridines with manganese dioxide and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. *Tetrahedron*, 51, 6511–6516. [http://dx.doi.org/10.1016/0040-4020\(95\)00318-3](http://dx.doi.org/10.1016/0040-4020(95)00318-3)
- Vanden Eynde, J. J., Mayence, A., & Maquestiau, A. (1992). A novel application of the oxidizing properties of pyridinium chlorochromate: Aromatization of Hantzsch 1,4-dihydropyridines. *Tetrahedron*, 48, 463–468. [http://dx.doi.org/10.1016/S0040-4020\(01\)89008-6](http://dx.doi.org/10.1016/S0040-4020(01)89008-6)
- Varma, R. S., & Kumar, D. (1999). Manganese triacetate mediated oxidation of Hantzsch 1,4-dihydropyridines to pyridines. *Tetrahedron Letters*, 40, 21–24. [http://dx.doi.org/10.1016/S0040-4039\(98\)80007-5](http://dx.doi.org/10.1016/S0040-4039(98)80007-5)
- Visentin, S., Rolando, B., Di Stilo, A., Fruttero, R., Novara, M., Carbone, E., ... Gasco, A. (2004). New 1,4-dihydropyridines endowed with NO-donor and calcium channel agonist properties. *Journal of Medicinal Chemistry*, 47, 2688–2693. <http://dx.doi.org/10.1021/jm031109v>
- Yadav, J. S., Subba Reddy, B. V., Sabitha, G., & Kiran Kumar Reddy, G. S. (2000). Aromatization of Hantzsch 1,4-dihydropyridines with 12-MeOH. *Synthesis*, 2000, 1532–1534. <http://dx.doi.org/10.1055/s-2000-7613>
- Zamponi, G. W., Stotz, S. C., Staples, R. J., Andro, T. M., Nelson, J. K., Hulubei, V., ... Natale, N. R. (2003). Unique structure–activity relationship for 4-isoxazolyl-1,4-dihydropyridines. *Journal of Medicinal Chemistry*, 46, 87–96. <http://dx.doi.org/10.1021/jm020354w>
- Zarghi, A., Sadeghi, H., Fassihi, A., Faizi, M., & Shafiee, A. (2003). Synthesis and calcium antagonist activity of 1,4-dihydropyridines containing phenylaminoimidazolyl substituents. *Il Farmaco*, 58, 1077–1081. [http://dx.doi.org/10.1016/S0014-827X\(03\)00159-9](http://dx.doi.org/10.1016/S0014-827X(03)00159-9)
- Zeynizadeh, B., Dilmaghani, K. A., & Mirzaei, M. (2007). Mild and convenient method for aromatization of Hantzsch esters of 1,4-dihydropyridines with Ag<sub>2</sub>O. *Acta Chimica Slovenica*, 54, 366–369.
- Žmitek, K., Zupan, M., Stavber, S., & Iskra, J. (2006). Iodine as a catalyst for efficient conversion of ketones to gem-dihydroperoxides by aqueous hydrogen peroxide. *Organic Letters*, 8, 2491–2494. <http://dx.doi.org/10.1021/ol060590r>
- Žmitek, K., Zupan, M., Stavber, S., & Iskra, J. (2007). The effect of iodine on the peroxidation of carbonyl compounds. *The Journal of Organic Chemistry*, 72, 6534–6540. <http://dx.doi.org/10.1021/jo0708745>
- Zolfigol, M. A., Ghorbani Choghmarani, A., Shahamirian, M., Safaiee, M., Mohammadpoor-Baltork, I., Mallakpour, S., & Abdollahi-Alibeiki, M. (2005). 4-Phenyl-1,2,4-triazole-3,5-dione as a novel and reusable reagent for the aromatization of 1,4-dihydropyridines under mild conditions. *Tetrahedron Letters*, 46, 5581–5584. <http://dx.doi.org/10.1016/j.tetlet.2005.06.031>



© 2015 The Author(s). This open access article is distributed under a Creative Commons Attribution (CC-BY) 4.0 license.

You are free to:

Share — copy and redistribute the material in any medium or format

Adapt — remix, transform, and build upon the material for any purpose, even commercially.

The licensor cannot revoke these freedoms as long as you follow the license terms.

Under the following terms:

Attribution — You must give appropriate credit, provide a link to the license, and indicate if changes were made.

You may do so in any reasonable manner, but not in any way that suggests the licensor endorses you or your use.

No additional restrictions

You may not apply legal terms or technological measures that legally restrict others from doing anything the license permits.

