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

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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*

Abstract: Trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxalane (DHPDMDO)/NH₄Br/ 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.

Keywords: Trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxalane; 1,4-dihydropyridines; NH₄Br; 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, & Ghafari, 2003; Khadilkar & Borkar, 1998; Litvić et al., 2005; Maquestiau, Mayence, & Eynede, 1991; Mashraqui & Karnik, 1998; Nakamichi, Kawashita, & Hayashi, 2002; Pfister, 1990; Sabitha, Kiran Kumar Reddy, Srinivas, Fatima, & Yadav, 2003; Sausins & Duburs, 1988; Vanden Eynede, Delfosse, Mayence, & Van Haverbeke, 1995; Vanden Eynede, 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;
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), CrO3 (Sausins & Duburs, 1988), MnO2 (Vanden Eynde et al., 1995), PCC (Vanden Eynde et al., 1992), Zr(NO3)4 (Sabitha et al., 2003), Bi(NO3)3 (Mashraqui & Karnik, 1998), clay-supported cupric nitrate (Maquestiau et al., 1991), H2O2/Co(OAc)2 (Hashemi et al., 2003), Pb(OAc)4 (Litvić et al., 2005), RuCl3/O2 (Sausins & Duburs, 1988), ceric ammonium nitrate (CAN) (Pfister, 1990), Pd/C (Nakamichi et al., 2002), K2MnO4 (Eynde, D’Orazio, & Haverbeke, 1994) and MnO2 (Varma & Kumar, 1999). Also, some other oxidants such as DDQ (Vanden Eynde et al., 1995), heteropolyacid/NaNO2/SiO2 (Niknam, Zolfigol, Razavian, & Mohammadpoor, 2005), I2/MeOH (Yadav, Subba Reddy, Sabitha, & Kiran Kumar Reddy, 2000), nitric oxide (Itoh, Nagata, Okada, & Ohsawa, 1995), HNO3 (García, Delgado, Cano, & Alvarez, 1993) and SeO2 (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., 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, Veeranjaneyulu, & Ravikanth, 2007; Das, Veeranjaneyulu, Krishnaiah, & Balasubramaniam, 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-dioxolane (Scheme 1) and used it as a powerful oxidant in some organic reactions (Azarifar & Khosravi, 2010a; Azarifar & Khosravi, 2010b; Azarifar, Khosravi, & Soleimanei, 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 Br+ from NH4Br 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.
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 CH3CN (4 mL), SSA (100 mg) was added and stirring of the reaction mixture was continued for 5 min at room temperature. Then, aqueous 30% H2O2 (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 Mg2SO4, 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, 1H NMR, and 13C NMR spectroscopes. 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), NH4Br (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, DHPDMDO (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, Na2SO3 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 MgSO4, 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 −1; 1H NMR (90 MHz, CDCl 3) δ: 1.60 (s, 6H, Me), 2.67 (s, 2H, CH2), 8.45 (4H, br, peroxide Hydrogen). 13C NMR: (22.5 MHz, D2O) 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 (DHPDMO) 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, & Shaar, 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). DHPDMO 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/NH4Br/HOAc system in water/MeCN at room temperature (Scheme 2).

At first, the condition of the reaction (solvent, amount of oxidant and NH4Br) is studied and in terms of yield and reaction time, water/MeCN is selected as the best solvent and amounts of oxidant and NH4Br 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-realizing groups accelerate the reaction. Also, 1,4-DHP containing the furyl substitution as a heterocyclic substation has been successfully aromatized (Table 2, entry 18).

The suggested mechanism shown in Scheme 3 describes the in situ generation of Br+. 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) | NH₄Br (mmol) | HOAc (mmol) | Solventa | 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        | CHCl₃    | 60         | 70        |
| 8     | 0.3            | 0.1          | 0.05        | CCl₄     | 45         | 85        |
| 9     | 0.3            | 0.1          | 0.05        | THF      | 30         | 90        |
| 10    | 0.3            | 0.1          | 0.05        | H₂O/MeCN | 21         | 95        |
| 11    | 0.1            | 0.1          | 0.05        | H₂O/MeCN | 45         | 87        |
| 12    | 0.2            | 0.1          | 0.05        | H₂O/MeCN | 35         | 90        |
| 13    | 0.5            | 0.1          | 0.05        | H₂O/MeCN | 20         | 85        |
| 14    | 1              | 0.1          | 0.05        | H₂O/MeCN | 18         | 75        |

*Solvent in all entries is 5 mL, for entries 10–14: H₂O (3 mL) and MeCN (2 mL).

Table 2. Oxidative aromatization of 1,4-dihydropyridines to the corresponding pyridines by DHPDMDO/NH₄Br/HOAc system in water/MeCN at r.t.*

| Entry | Compound | R          | Time (min) | Yield (%)b | Mp (°C)  |
|-------|----------|------------|------------|-------------|----------|
| 1     | 2a       | H          | 12         | 96          | 67–69    |
| 2     | 2b       | CH₃        | 14         | 94          | Oil      |
| 3     | 2c       | CH₂CH₂     | 17         | 95          | Oil      |
| 4     | 2d       | CH₂CH₂CH₂  | 17         | 95          | Oil      |
| 5     | 2e       | Isopropyl- | 17         | 93          | 72–74    |
| 6     | 2f       | C₆H₅CH=CH  | 18         | 97          | Oil      |
| 7     | 2g       | C₆H₅       | 21         | 95          | 61–63    |
| 8     | 2h       | 4-NO₂-C₆H₅ | 20         | 95          | 114–116  |
| 9     | 2i       | 3-NO₂-C₆H₅ | 27         | 94          | Oil      |
| 10    | 2j       | 2-Cl-C₆H₅  | 30         | 96          | 72–74    |
| 11    | 2k       | 4-Cl-C₆H₅  | 27         | 98          | 61–63    |
| 12    | 2l       | 2,4-Cl₂-C₆H₃| 32         | 95          | 76–78    |
| 13    | 2m       | 3-Br-C₆H₅  | 31         | 93          | 72–74    |
| 14    | 2n       | 4-F-C₆H₅   | 35         | 97          | 92–94    |
| 15    | 2o       | 4-MeO-C₆H₅ | 26         | 94          | 50–52    |
| 16    | 2p       | 4-Me-C₆H₅  | 25         | 99          | 72–74    |
| 17    | 2q       | 4-HO-C₆H₅  | 20         | 93          | 170–172  |
| 18    | 2r       | 2-Furyl    | 31         | 92          | Oil      |

*Conditions: 1,4-DHPs (1 mmol), NH₄Br (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 (1H NMR, 13C NMR, and IR) analysis and compared with the data reported in the literature.

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

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

| Entry | Oxidant | Conditions | Solvent | Time (h) | Yield (%) | Reference |
|-------|---------|------------|---------|----------|-----------|-----------|
| 1     | DHPMDO/NH₄Br/HOAc | r.t | H₂O/MeCN | 0.35 | 95 | This method |
| 2     | Fe(ClO₄)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 | CH₂Cl₂ | 0.42 | 88 | Zolfigol et al. (2005) |
| 5     | Magtrieve TM (CrO₂) | Reflux | CHCl₃ | 2 | 97 | Ka and Kim (1999) |
| 6     | 9-Phenyl-10-methylacridinium | REFLUX, hv | MeCN | 12 | 96 | Fang et al. (2007) |
| 7     | Dess-Martin periodinane/ KBr | r.t | MeCN | 3 | 82 | Karade et al. (2008) |
| 8     | UHP/I₂ | r.t | AcOEt | 12 | 89 | Filipan-Litvić et al. (2008a) |
| 9     | Bismuth Nitrate Pentahydrate | r.t | AcOH | 7 | 90 | Mashraqui and Karnik (1998) |
| 10    | Ag₂O | Reflux | MeCN | 1.7 | 96 | Zeynizadeh et al. (2007) |
| 11    | Cu(C₂H₄N₂O₂) | Reflux | AcOH | 1 | 90 | Dehghanpour et al. (2007) |
| 12    | n-Butyltriphenylphosphonium peroxodisulfate | Reflux | MeCN | 0.25 | 87 | Gorjizadeh and Abdollahi-Alibeik (2011) |
| 13    | Pd/C | 80 C | AcOH | 2 | 97 | Nakamichi et al. (2002) |
| 14    | Mn(pbda)₂Cl₂/Al-MCM-41 | Reflux | AcOH | 2 | 89 | Heravi et al. (2009) |
| 15    | H₃PMo₁₀V₆O₄₀ | Reflux | AcOH | 1.1 | 96 | Heravi et al. (2007) |
| 16    | S-Nitrosoglutathione | r.t | MeCN/H₂O | 10 | 70 | Mao et al. (2009) |
| 17    | VOCl₃ | r.t | CH₂Cl₂ | 1 | 97 | Filipan-Litvić et al. (2008b) |

r.t stands for room temperature.
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/NIH_3Br/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.

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