A Convenient Synthesis of Oxazolines and Imidazolines from Aromatic Aldehydes with Pyridinium Hydrobromide Perbromide in Water

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Abstract: Various 2-oxazolines were prepared from aromatic aldehydes and 2-aminoethanol with pyridinium hydrobromide perbromide in water at room temperature. 2-Imidazolines were also obtained in good yields from aromatic aldehydes and ethylenediamine under the same reaction conditions.

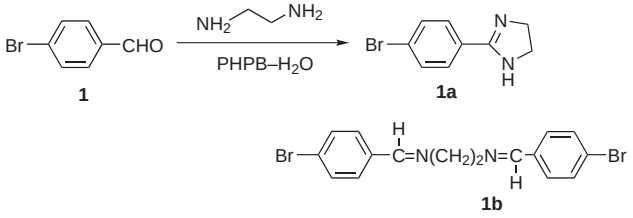
Key words: oxazoline, imidazoline, pyridinium hydrobromide perbromide, aldehyde, 2-aminoethanol, ethylenediamine

Various oxazoline and imidazoline derivatives are known to be important heterocyclic compounds for their biological activities.[1] Further, those compounds are also useful for the synthesis of many functional compounds as key intermediates[2,3] and excellent catalyst ligands.[4] Many useful methods for the synthesis of oxazolines[1c,5] and imidazolines[1e,5b,6] have been reported previously. However, some of these methods involve disadvantages such as acidic conditions and the use of complex reagents in organic solvents. Therefore, there is still considerable interest in investigating other convenient and chemoselective synthetic methods of oxazolines and imidazolines without using organic solvents in terms of economic benefit, environmental impact and safety.

On the other hand, ammonium tribromides such as pyridinium hydrobromide perbromide (PHPB) and phenyltrimethylammonium tribromide (PTAB) were reported to be convenient and chemoselective for the oxidation of 1,2-diols, secondary alcohols, and Tishchienko-like esterification of aliphatic alcohols in previous papers.[7,8] As tribromides are much easier to handle and they maintain the desired stoichiometry in comparison with Br_2 and other oxidative reagents,[7–9] the use of commercially available PHPB, PTAB has been more advantageous and attractive than that of other complex reagents in organic synthesis. We considered it interesting to find a new simple procedure for preparation of oxazoline and imidazoline derivatives from aldehydes with tribromides without using organic solvents. We would like to report the results of our studies concerning the conversion of aldehydes to 2-substituted oxazoline and imidazoline derivatives with PHPB or PTAB in water.

At first, the reaction of 4-bromobenzaldehyde (**1**), chosen as a representative aldehyde for this study, was carried out with PHPB and ethylenediamine in water at room temperature. The results are summarized in Table 1. At 1.0 molar ratio of PHPB over **1** in the presence of 6.0 molar equivalents of ethylenediamine, 2-(4-bromophenyl)imidazoline **1a** was mainly obtained, while the yield of **1a** was not fully satisfactory accompanied by diimine **1b** (run 1). At more than 2.0 molar equivalents of PHPB over **1**, imidazoline **1a** was obtained in good yields (runs 2–4).

Table 1 Reaction of 4-Bromobenzaldehyde and Ethylenediamine with PHPB in H_2O[a]



Run	Molar ratio (**1**) PHPB	Time (h)	Product and yield (%) **1a**	**1b**
1	1.0	14	68	21
2	2.0	15	88	4
3	3.0	15	90	2
4	4.0	16	90	trace
5	0.0	40	–	96
6	0.0[b]	15	–	82[c]
7	0.0[d]	15	–	90[e]
8	0.0[f]	15	90	–

[a] Reagents and conditions: **1** (0.25 mmol), ethylenediamine (1.5 mmol), H_2O (6 mL), r.t.
[b] Bu_4NBr: 0.75 mmol.
[c] Recovered **1**: 14%.
[d] PyHBr: 0.5 mmol.
[e] Recovered **1**: 3%.
[f] PTAB: 0.5 mmol.

To examine the effect of PHPB, the reaction of **1** and ethylenediamine was carried out without using PHPB. Imidazoline **1a** was not obtained, while only diimine **1b** was mainly obtained (run 5). With Bu_4NBr or PyHBr in place of PHPB, diimine **1b** and recovered **1** were obtained (runs 6, 7). On the contrary, the reaction of **1** and ethylenediamine with PTAB afforded imidazoline **1a** in 90% yield

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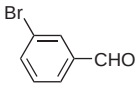
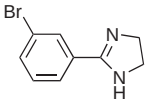
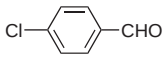
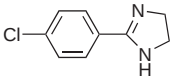
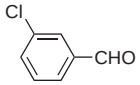
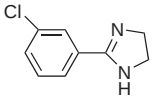
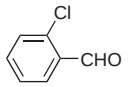
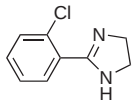
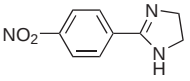
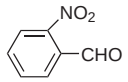
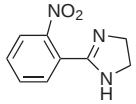
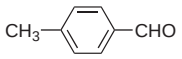
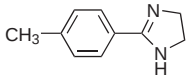
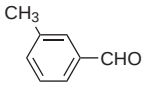
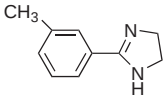
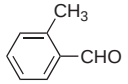
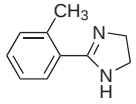
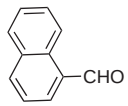
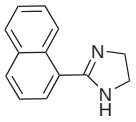
under the same reaction conditions (run 8). Tribromides PHPB and PTAB were ascertained to be essential for obtaining imidazoline **1a** in good yields. As PHPB is more soluble in water than PTAB, the use of PHPB is expected to be more suitable for this synthetic method than PTAB.

To exhibit the solvent effect of water in this method, the reaction of **1** and ethylenediamine with PHPB was carried out in CH_2Cl_2, hexane under the same reaction conditions. Aldehyde **1** was recovered unchanged in 50–84% yields accompanied by imidazoline **1a** (5–24%), respectively. The reaction of **1** and ethylenediamine with PHPB was also carried out with other polar solvents such as methanol, acetonitrile, and acetic acid. Dimethyl acetal (71%) was mainly obtained accompanied by imidazoline **1a** (21%) in methanol. A mixture of imidazoline **1** (56%) and diimine **1b** (27%) was afforded in acetonitrile. The

Table 2 Reaction of Arylaldehyde and Ethylenediamine with PHPB in H_2O[a]

Run	Substrate (**S**)	Molar ratio (**S**) PHPB	Time (h)	Product	Yield (%)
1	 **2**	2.0	12	 **2a**	80
2	 **3**	3.0	24	 **3a**	82
3	 **4**	2.0	19	 **4a**	90
4	 **5**	2.0	19	 **5a**	89
5	 **6**	3.0	18	 **6a**	83
6	 **7**	2.0	15	 **7a**	90
7	 **8**	2.0	16	 **8a**	78
8	 **9**	2.0	19	 **9a**	82
9	 **10**	2.0	22	 **10a**	82
10	 **11**	2.0	23	 **11a**	72

[a] Reagents and conditions: Substrate (**S**, 0.25 mmol), $H_2N(CH)_2NH_2$ (1.5 mmol), H_2O (6 mL), r.t.

reaction of **1** and ethylenediamine with PHPB in acetic acid did not take place to give imidazoline **1** and diimine **1b**. In the present experiments, water was found to be more useful for the conversion of aldehydes to imidazolines than other organic solvents in this method.

To clarify the limitations and chemoselectivity for this conversion of aldehyde to imidazolines, the reaction of various aldehydes and ethylenediamine with PHPB was examined under the same reaction conditions. The results are summarized in Table 2. The reaction of benzaldehydes **2**–**5** with PHPB in the presence of ethylenediamine afforded the corresponding 2-substituted imidazolines **2a**–**5a** in good yields (runs 1–4).

Nitrobenzaldehydes **6**, **7**, tolualdehydes **8**–**10**, and 1-naphthaldehyde (**11**) were also converted to respective imidazolines **6a**–**11a** (runs 5–10). On the other hand, acetophenone, benzophenone were recovered unchanged in over 70% yields, respectively.[10] Thus, the method of PHPB in water was found to be convenient and chemoselective for conversion of aromatic aldehydes to 2-substituted imidazolines in the presence of ethylenediamine.

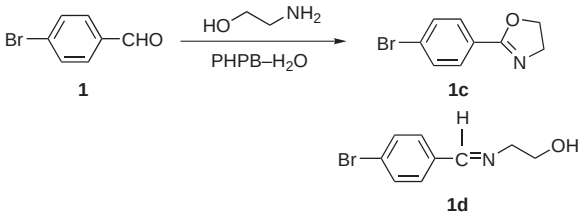
Further, 2-substituted oxazoline derivatives have been well recognized as useful catalyst ligands in synthetic organic chemistry.[4] Therefore, convenient conversion of aldehydes to 2-oxazoline derivatives was also considered an intriguing study area.

At first, the reaction of 4-bromobenzaldehyde (**1**), chosen as a representative aldehyde for this study, was also carried out with PHPB and 2-aminoethanol under the same reaction conditions. The results are summarized in Table 3. At 1.0–2.0 molar equivalents of PHPB over aldehyde **1**, a mixture of 2-(4-bromophenyl)oxazoline (**1c**), hydroxyimine (**1d**), and recovered **1** was afforded (runs 1, 2). 2-Substituted oxazoline **1c** was obtained in good yield at 3.0 molar equivalents of PHPB over **1** (run 3). Accordingly, more than 2.0 molar equivalents of PHPB over aldehydes were needed to obtain 2-substituted oxazolines in high yields.

To examine the utility of PHPB in this method, the reaction of 4-bromobenzaldehyde (**1**) without using PHPB was carried out under the same reaction conditions. Hydroxyimine **1d** was mainly obtained accompanied by recovered **1** (run 4). To clarify the effect of tribromide, the reaction of **1** with Bu_4NBr, PyHBr in place of PHPB was also carried out. Hydroxyimine **1d** was afforded predominantly. Oxazoline **1c** was not obtained (runs 5, 6). On the contrary, the reaction of aldehyde **1** and 2-aminoethanol with PTAB afforded oxazoline **1c** (run 7). Accordingly, tribromides PHPB and PTAB were also found to be useful for preparation of oxazoline from aldehyde as well as the above-mentioned synthesis of imidazoline.

Further, to examine the solvent effect of H_2O, the reaction of **1** with PHPB in CH_2Cl_2, hexane in the presence of 2-aminoethanol was carried out under the same reaction conditions. The yields of oxazoline **1c** were less satisfactory, while aldehyde **1** was recovered in 50–84% yields. The reaction of **1** and 2-aminoethanol with PHPB was also carried out in other polar solvents such as methanol, acetonitrile, and acetic acid. Dimethyl acetal (72%) was mainly obtained accompanied by oxazoline **1c** (19%) in methanol. A mixture of oxazoline **1c** (65%) and recovered **1** (26%) was afforded in acetic acid. On the contrary, oxazoline **1c** (90%) was obtained in acetonitrile. Consequently, H_2O and a polar solvent such as acetonitrile were more effective for the conversion of aldehydes to oxazolines than other solvents. In this synthetic method, H_2O was supposed to be particularly convenient and suitable for the conversion of aldehyde to 2-substituted oxazolines in view of the environmental impact and safety.

Table 3 Reaction of 4-Bromobenzaldehyde and 2-Aminoethanol with PHPB in H_2O[a]



1 **1c** **1d**

Run	Molar ratio (**1**) PHPB	Time (h)	Product **1c**	Product **1d**	Yield (%) Recovered
1	1.0	25	28	54	13
2	2.0	23	62	22	11
3	3.0	23	89	–	4
4	0.0	69	–	73	17
5	0.0[b]	66	–	89	6
6	0.0[c]	66	–	88	8
7	0.0[d]	23	65	21	6

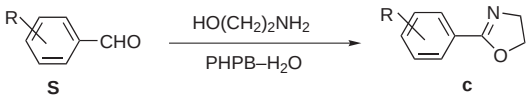
[a] Reagents and conditions: **1** (0.25 mmol), 2-aminoethanol (1.5 mmol), H_2O (6 mL), r.t.
[b] Bu_4NBr: 0.75 mmol.
[c] PyHBr: 0.75 mmol.
[d] PTAB: 0.5 mmol.

The reaction of various aromatic aldehydes under the same reaction conditions was carried out to elucidate the limitations and chemoselectivity for the conversion of aldehydes to 2-substituted oxazolines by PHPB–H_2O. The results are shown in Table 4. The reaction of aldehydes **2**–**7** took place to give the corresponding 2-substituted oxazolines **2c**–**7c** in good yields, as expected (runs 1–6). The *p*- and *m*-tolualdehydes **8** and **9** were also converted to respective oxazolines **8c** and **9c** in good yields, while the reaction of *o*-tolualdehyde **10** afforded oxazolines **10c** (58%) accompanied by recovered **10** (23%, runs 7–9).[11] 1-Naphthaldehyde (**11**) and 3,4-dimethylbenzaldehyde (**12**) were also converted to oxazolines **11c** and **12c** (runs 10, 11). The reaction of terephthalaldehyde (**13**), isophthalaldehyde (**14**) with 3.0–4.0 molar equivalents of PHPB over dialdehydes **13** and **14** afforded the corresponding

dioxazoline derivatives **13c** and **14c** in good yields (runs 12, 13). On the contrary, phthalaldehyde was not converted to the corresponding dioxazoline under the same reaction conditions.[12]

The following reaction of various carbonyl compounds such as nonanal, cyclooctanone, acetophenone was carried out to clarify the chemoselectivity and limitations of this method. The reaction of nonanal with PHPB in the presence of 2-aminoethanol afforded a complex mixture of nonanal (ca. 50%) and respective hydoxyimine (ca. 20%).[13] The reaction of cyclooctanone also took place to give a mixture of hydroxyimine (22%) and recovered cyclooctanone (70%). Acetophenone was converted to hydroxyimine (67%) accompanied by recovered acetophenone (23%). Benzophenone (92%) was recovered unchanged under the same reaction conditions. Consequently, PHPB–H_2O in the presence of the 2-aminoethanol system was chemoselective for the conversion of aromatic aldehydes to 2-substituted oxazolines easily.

Table 4 Reaction of Arylaldehyde and 2-Aminoethanol with PHPB in H_2O[a]



S **c**

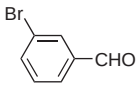
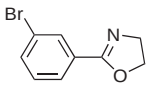
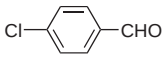
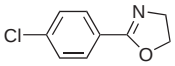
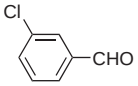
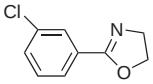
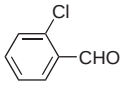
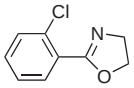
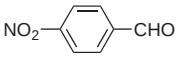
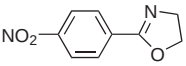
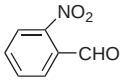
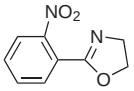
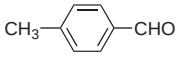
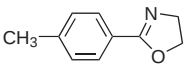
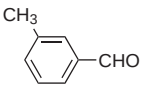
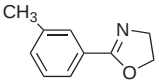
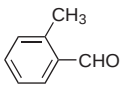
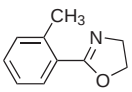
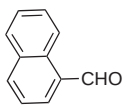
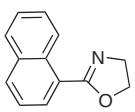
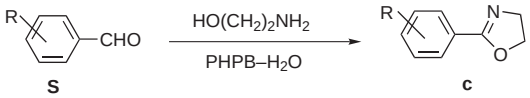
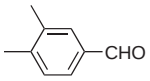
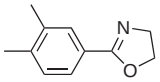
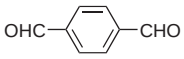
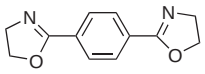
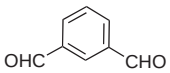
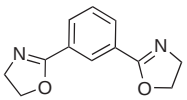
Run	Substrate (**S**)	Molar ratio (**S**) PHPB	Time (h)	Product	Yield (%)
1	 **2**	2.0	18	 **2c**	89
2	 **3**	2.0	14	 **3c**	95
3	 **4**	2.0	19	 **4c**	90
4	 **5**	3.0	13	 **5c**	81[b]
5	 **6**	3.0	18	 **6c**	95
6	 **7**	2.0	15	 **7c**	70[c]
7	 **8**	2.0	14	 **8c**	87
8	 **9**	2.0	14	 **9c**	85
9	 **10**	2.0	14	 **10c**	58[d]
10	 **11**	2.0	21	 **11c**	72[e]

Table 4 Reaction of Arylaldehyde and 2-Aminoethanol with PHPB in H_2O[a] (continued)



S **c**

Run	Substrate (**S**)	Molar ratio (**S**) PHPB	Time (h)	Product	Yield (%)
11	 **12**	2.0	19	 **12c**	92
12	 **13**	4.0[f]	40	 **13c**	91[g]
13	 **14**	3.0[h]	39	 **14c**	83[i]

[a] *Reagents and conditions*: substrate (**S**, 0.25 mmol), $HO(CH)_2NH_2$ (1.5 mmol), H_2O (6 mL), r.t.
[b] Recovered **5**: 16%.
[c] Hydroxyimine: 25%.
[d] Recovered **10**: 23%.
[e] Recovered **11**: 15%.
[f] $HO(CH_2)_2NH_2$: 3.0 mmol.
[g] Monoaldehydeoxazoline: 2%.
[h] $HO(CH_2)_2NH_2$: 2.2 mmol.
[i] Monoaldehydeoxazoline: 10%.

In conclusion, PHPB–H_2O in the presence of an ethylenediamine system was found to be a simple and chemoselective method for the transformation of various aromatic aldehydes into 2-substituted imidazolines without overoxidation to carboxylic acid.[1e,5b,6,14] Furthermore, the PHPB–H_2O system in the presence of 2-aminoethanol was also confirmed to be an alternative convenient and chemoselective procedure for the conversion of aromatic aldehydes to 2-substituted oxazolines.[1c,5,15]

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(10) The reaction of ethylenediamine and aromatic dialdehydes such as terephthalaldehyde, isophthalaldehyde, and phthalaldehyde with PHPB took place to give no respective diimidazilines under the same reaction conditions.

(11) It was assumed that steric hindrance between the formyl group and the methyl group exerted influence on the decrease in the yield of the corresponding oxazoline.

(12) The products were complicated. The steric hindrance of two formyl groups in phthalaldehyde was supposed to inhibit generation of the respective dioxazoline.

(13) The yields of nonanal (ca. 50%) and hydroxyimine (ca. 20%) were determined by ^{1}H NMR analysis of crude products.

(14) **Typical Procedure for Preparation of Imidazoline from Aldehyde.**
To a solution of 4-bromobenzaldehyde (**1**, 46 mg, 0.25 mmol) in H_2O (6 mL) were added PHPB (160 mg, 0.5 mmol). Etylenediamine [90 mg (100 μL), 1.5 mmol] was added. After stirring for 15 h at r.t., the reaction mixture was treated with 0.5 M aq $Na_2S_2O_3$ and extracted with EtOAc. The organic layer was washed with 0.5 M aq $Na_2S_2O_3$ and successively washed with sat. aq NaCl and dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by column chromatography on silica gel (Wakogel C-200) with $CHCl_3$. Imidazoline **1a** (50 mg, 0.22 mmol) was obtained in 88% yield.

(15) **Typical Procedure for Preparation of Oxazoline from Aldehyde.**
To a solution of 4-bromobenzaldehyde (**1**, 46 mg, 0.25 mmol) in H_2O (6 mL) were added PHPB (240 mg, 0.75 mmol). 2-Aminoethanol [92 mg (90 μL), 1.5 mmol] was added. After stirring for 23 h at r.t., the reaction mixture was treated with 0.5 M aq $Na_2S_2O_3$ and extracted with EtOAc. The organic layer was washed with 0.5 M aq $Na_2S_2O_3$ and successively washed with sat. aq NaCl and dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by column chromatography on silica gel (Wakogel C-200) with $CHCl_3$. Oxazoline **1c** (50 mg, 0.22 mmol) was obtained in 89% yield.