A Facile and Efficient Synthesis of 2-Imidazolines from Aldehydes Using Hydrogen Peroxide and Substoichiometric Sodium Iodide

Guo-yi Bai,* Kai Xu, Guo-feng Chen, Yong-hui Yang, Tian-yu Li

Key Laboratory of Chemical Biology of Hebei Province, College of Chemistry and Environmental Science, Hebei University, Baoding 071002, P. R. of China
Fax +86(312)5937102; E-mail: gybai@hbu.edu.cn
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Abstract: The reaction of aldehydes with ethylenediamine for the preparation of 2-imidazolines has been studied using hydrogen peroxide as an oxidant in the presence of sodium iodide and anhydrous magnesium sulfate. A mild, green, and efficient method is established to carry out this reaction in high yield.

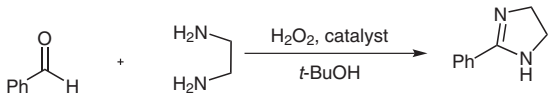
Key words: 2-imidazoline, hydrogen peroxide, aldehydes, ethylenediamine, environmentally friendly process

The synthesis of 2-imidazolines has attracted much interest, not only because they are important intermediates, chiral ligands, and chiral auxiliaries in organic reactions,[1] but also because they have found wide applications in many biological areas including antidiabetic and antiparasitic activities.[2] Nitriles are generally employed as the starting materials to prepare these compounds,[3] but this method has shortcomings, such as high reaction temperatures, acidic conditions, and the use of highly toxic cyanide. An alternative method, using carboxylic acids and derivatives as the starting substrates, gives 2-imidazolines with low yields or requires extended reaction times.[4] Recently, aldehydes and ethylenediamine have been used as starting materials in the preparation of 2-imidazolines.[5] Ishihara has communicated that the synthesis can be performed by the reaction of aldehydes with ethylenediamine in the presence of 1.25 equivalents of molecular iodine.[5a] Fujioka used 1.05 equivalents of *N*-halosuccinimides (X = Cl, Br, and I)[5b] and Sayama used 2–3 equivalents of pyridinium hydrobromide perbromide in the same conversion.[5e] However, these methods are restricted by the use of expensive and environmentally unfriendly halide reagents (iodine, NBS/NIS/NCS, or pyridinium hydrobromide perbromide) as oxidants. This shortcoming has limited their practical application and there has been great demand for the use of a green oxidant.

Against this context, our interest has centered on hydrogen peroxide, which is a universal, ecologically clean, and convenient reagent for a series of oxidations in organic synthesis.[6] In this paper, we report our studies on the effective and green synthesis of 2-imidazolines from aldehydes and ethylenediamine via a new hydrogen peroxide oxidation system. In this system, the use of halides has been drastically reduced; hydrogen peroxide being used as the major oxidant with only a small amount of sodium iodide as catalyst.

Initially, the synthesis of 2-phenylimidazoline from benzaldehyde and ethylenediamine was carried out with different hydrogen peroxide systems. The reaction mixtures were first analyzed by gas chromatography. Unfortunately, 2-phenylimidazoline could not be detected in the reaction mixtures when hydrogen peroxide was used alone or with ceric ammonium nitrate (CAN) as the oxidant (Table 1, entries 1, 3). Only the Schiff base from the reaction of benzaldehyde and ethylenediamine was obtained when hydrogen peroxide was used alone, suggesting that hydrogen peroxide is not suitable for the transformation of the Schiff base intermediate to 2-imidazoline. On the other hand, benzoic acid was the only product when hydrogen peroxide/CAN system was used as the oxidant. However, some other hydrogen peroxide systems such as

Table 1 Preparation of 2-Phenylimidazoline from Benzaldehyde and Ethylenediamine[a]



1 2

Entry	Catalyst	Yield (%)[b]
1	none	0
2	KI	21
3	CAN	0
4	NaI[c]	6
5	NaI	33
6	NaI[d]	29
7	NaI[c,e]	5
8	NaI[e]	31
9	NaI[c,f]	0

[a] Reaction conditions: benzaldehyde (1 mmol), ethylenediamine (1.1 mmol), *t*-BuOH (10 mL), catalyst (0.4 mmol), 80 °C.
[b] Determined by GC.
[c] H_2O_2 was added in one portion.
[d] At 50 °C.
[e] Ultrasound 40 KHz was used at 50 °C for 3 h.
[f] Microwave 150 W was used at 50 °C for 20 min.

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hydrogen peroxide with potassium iodide (entry 2) and hydrogen peroxide with sodium iodide (entry 5) were found to have better oxidative performance in this reaction. In particular, hydrogen peroxide with sodium iodide showed the highest activity among these systems.

In the optimization, several solvents, including *tert*-butyl alcohol, ethyl acetate, ethanol, and water were tested and the best result was achieved using *tert*-butyl alcohol. Moreover, the manner of addition of the hydrogen peroxide was also studied. A slow addition of hydrogen peroxide gave higher yields than addition as a single portion (entries 4, 5).

Application of ultrasound and microwave heating can often cut down the reaction time dramatically.[7] Unfortunately, the results showed that both ultrasound (entries 7, 8) and microwave (entry 9) confer no great advantage to this reaction compared with the traditional heating method.

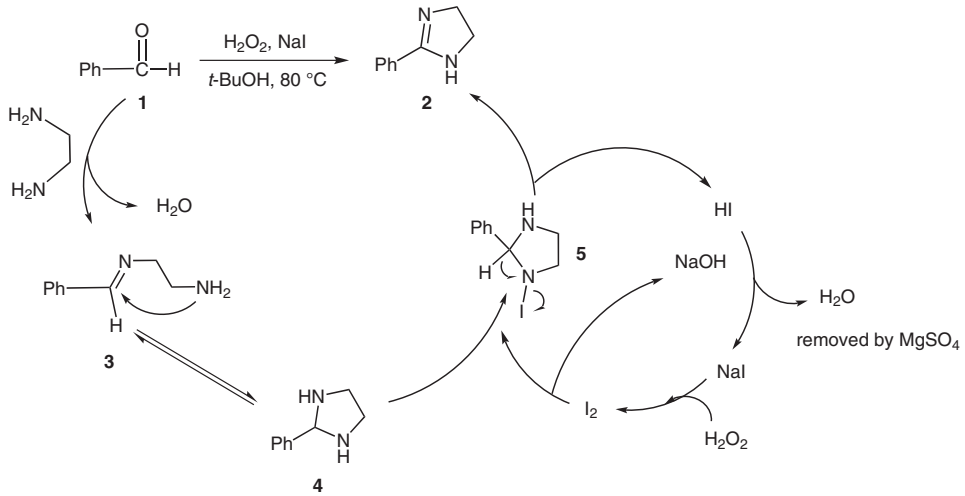
The effect of temperature was also examined and a higher yield was obtained at 80 °C than at 50 °C or at reflux. Thus, the ratios of the reactants were optimized at 80 °C to maximize the yield of the reaction. A ratio of 1:1.1:0.8 for benzaldehyde/ethylenediamine/sodium iodide was found to be optimum for the reaction and the yield of 2-phenylimidazoline under these conditions was 74% (Table 2, entry 3), although still lower than our expectations. The main reason for this result was attributed to the water generated in situ from the formation of the Schiff base intermediate and the decomposition of hydrogen peroxide, preventing the desired transformation. Therefore, we attempted several methods to remove the water including azeotropic removal with toluene, and addition of different types of drying agents such as molecular sieves type 4Å, anhydrous magnesium sulfate, and anhydrous sodium sulfate. It was found that addition of a small amount of anhydrous magnesium sulfate could markedly improve the yield. Thus, addition of anhydrous magnesium sulfate to a mixture of benzaldehyde and ethylenediamine in the presence of hydrogen peroxide and sodium iodide was examined in detail for the synthesis of 2-phenylimidazoline. Noticeably, the yield increased greatly from 74% to 97% on adding 0.50 gram of anhydrous magnesium sulfate to the original system (entries 3, 10) and it is the best result among all the runs. On the other hand, the yield was also 94% on reducing the amount of sodium iodide to 0.4 mmol (entry 8) and so we opted to use 0.4 mmol of sodium iodide as the appropriate amount for the purpose of green synthesis.

Table 2 The Effect of Anhydrous Magnesium Sulfate and Sodium Iodide[a]

Entry	$MgSO_4$ (g)	NaI (mmol)	Yield (%)[b]
1	0	0.4	33
2	0	0.6	69
3	0	0.8	74
4	0	1.0	61
5	0.25	0.4	79
6	0.50	0	0
7	0.50	0.2	77
8	0.50	0.4	94
9	0.50	0.6	96
10	0.50	0.8	97
11	0.50	1.0	97
12	0.75	0.4	87
13	1.00	0.4	86

[a] Reaction conditions: benzaldehyde (1 mmol) and ethylenediamine (1.1 mmol) in *t*-BuOH (10 mL), 80 °C.
[b] Determined by GC.

The color of the reaction mixture quickly changed to deep yellow, as iodine was initially generated after the addition of hydrogen peroxide to the mixture, and then slowly disappeared. A detailed mechanism of the reaction is pro-



Scheme 1 Proposed mechanism for the synthesis of 2-phenylimidazoline in the H_2O_2/NaI/$MgSO_4$ system

posed based on the above experimental phenomenon and results, as shown in Scheme 1. Firstly, the intermediate **4** is formed via cyclization of the Schiff base intermediate **3**, obtained from the corresponding aldehyde and ethylenediamine without any catalyst, as Fujioka has described.[5b] Then, **4** reacts with the in situ generated iodine, from the oxidation of sodium iodide by hydrogen peroxide, to form the key intermediate **5**, as Gogoi[5c] and Ishihara[5d] have described, which then eliminates hydrogen iodide to generate the desired imidazoline. The hydrogen iodide is neutralized by sodium hydroxide, which is the by-product of the reaction of sodium iodide and hydrogen peroxide, to regenerate the sodium iodide catalyst and water. Finally, the water is removed by anhydrous magnesium sulfate and the hydrogen peroxide oxidation process can recycle effectively.

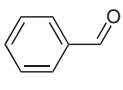
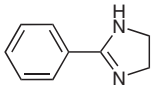
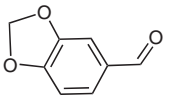
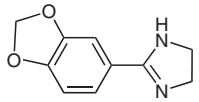
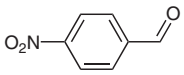
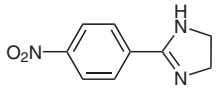
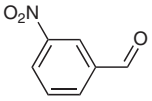
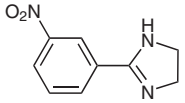
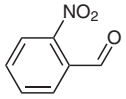
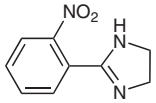
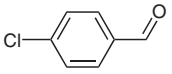
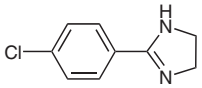
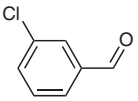
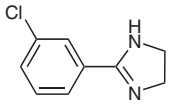
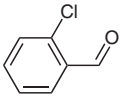
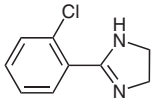
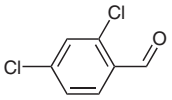
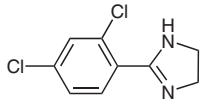
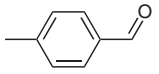
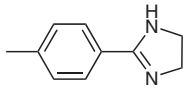
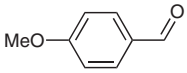
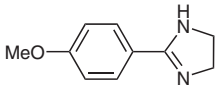
The ineffectiveness of the ultrasound and microwave irradiation can be ascribed to the fact that both can accelerate the decomposition of hydrogen peroxide rather than its reaction with sodium iodide.

Based on the above results, a series of aldehydes were treated with ethylenediamine in the presence of hydrogen peroxide/sodium iodide/anhydrous magnesium sulfate under the same conditions to provide the corresponding 2-imidazolines in moderate to excellent yields, as shown in Table 3.

As listed in Table 3, it can be seen that most of the reactions between the aldehydes with ethylenediamine with the hydrogen peroxide/sodium iodide/anhydrous magnesium sulfate system proceeded smoothly to give the corresponding 2-imidazolines in good yields. Reactions of substrates possessing both electron-withdrawing (entries 3, 6) and electron-donating (entries 2, 10, 11) groups proceeded well, with the yields all above 91%. Thus, electronic effects seem not to be prominent in this reaction. Moreover, steric effects on the benzene ring were also perceived. The *o*-substituted aldehydes (entries 5, 8) gave rather lower yields than the *m*- and *p*-substituted aldehydes (entries 4, 7 and entries 3, 6), suggesting that the main effect is steric factor rather than electronic.

In summary, the hydrogen peroxide/sodium iodide system has been employed as a novel, mild, and efficient means for the preparation of 2-imidazolines from aldehydes and ethylenediamine in excellent yields in the presence of anhydrous magnesium sulfate. In addition, the reactions proceed under environmentally friendly conditions.

Table 3 2-Imidazolines Prepared[a]

Entry	Aldehyde	Product	Yield (%)[b,c]
1			96
2			quant
3			97
4			74
5			62
6			99
7			98
8			89
9			88
10			94
11			91

[a] Reaction conditions: aldehyde (1 mmol), ethylenediamine (1.1 mmol), NaI (0.4 mmol), and $MgSO_4$ (0.5 g) in *t*-BuOH (10 mL), 80 °C.

[b] Isolated yield.

[c] All the products were confirmed by mp, ^{1}H NMR, ^{13}C NMR, and IR data (see experimental), which corresponded to the reported materials.[5c,h,8–12]

Sonication was performed in Kunshan KQ-300VDE ultrasonic cleaner, the microwave reactions were carried out in DISCOVER S-Class chemical synthesis system of CEM Corporation. Flash column chromatography was performed on silica 200–300 mesh. Melting points were measured with a XT-4 melting point apparatus and are uncorrected. Reaction mixtures were analyzed by gas chromatography using a 30 m SE-30 capillary column. IR spectra were recorded on a Varian 640-FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded at 600 MHz and 150 MHz, respectively, on a Bruker spectrometer in $CDCl_3$ or DMSO-d_6 using TMS as the internal standard. Mass spectra were recorded on Bruker APEX-Ultra 7.0-T spectrometer.

2-Imidazolines; General Procedure

A mixture of aldehyde (1.0 mmol), ethylenediamine (1.1 mmol), and *t*-BuOH (10 mL) was stirred for 20 min in a round-bottomed flask (25 mL). NaI (0.06 g, 0.4 mmol) and anhyd $MgSO_4$ (0.5 g) were then added and this mixture was kept at 80 °C with stirring. During this time aq 30% H_2O_2 was added dropwise slowly until the color of I_2 was not discharged. After workup, the reaction mixture was quenched with sat. aq $Na_2S_2O_4$ (2 mL) and the precipitate was

collected by filtration. The products were purified by column chromatography on silica gel using EtOAc–Et_3N (100:1) as eluent (Table 3).

2-Phenylimidazoline
Yield: 96%; mp 99–101 °C (Lit.[9] mp 100–101 °C).

IR (KBr): 3196, 2925, 1604, 1507, 1266, 979, 694 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 7.1 Hz, 2 H), 7.45 (t, *J* = 7.3 Hz, 1 H), 7.40 (t, *J* = 7.4 Hz, 2 H), 5.06 (s, 1 H), 3.77 (s, 4 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.74, 130.56, 130.53, 128.41, 126.96, 50.29.

2-(1, 3-Benzodioxol-5-yl)imidazoline
Yield: quant; mp 178–180 °C (Lit.[12] mp 178 °C).

IR (KBr): 3174, 2928, 2788, 1580, 1035, 925, 825 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 1.7 Hz, 1 H), 7.28–7.23 (m, 1 H), 6.81 (d, *J* = 8.1 Hz, 1 H), 6.01 (s, 2 H), 4.66 (s, 1 H), 3.77 (s, 4 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 162.48, 148.20, 146.52, 124.20, 120.92, 107.24, 106.53, 100.79, 48.99.

2-(4-Nitrophenyl)imidazoline
Yield: 97%; mp 232–234 °C (Lit.[5c] mp 231 °C).

IR (KBr): 3176, 2937, 1581, 1520, 1336, 1108, 858 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 8.8 Hz, 2 H), 7.95 (d, *J* = 8.8 Hz, 2 H), 4.80 (s, 1 H), 4.07 (s, 2 H), 3.65 (s, 2 H).

^{13}C NMR (150 MHz, DMSO-d_6): d = 162.65, 148.85, 136.89, 128.81, 123.94, 49.97.

2-(3-Nitrophenyl)imidazoline
Yield: 74%; mp 158–159 °C (Lit.[9] mp 156–157 °C).

IR (KBr): 3145, 2933, 1597, 1521, 1348, 860, 698 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.59 (s, 1 H), 8.31 (d, *J* = 8.5 Hz, 1 H), 8.18 (d, *J* = 7.8 Hz, 1 H), 7.61 (t, *J* = 8.0 Hz, 1 H), 4.88 (s, 1 H), 3.86 (s, 4 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 162.62, 148.19, 133.04, 132.24, 129.58, 125.20, 121.90, 50.44.

2-(2-Nitrophenyl)imidazoline
Yield: 62%; mp 96–98 °C (Lit.[10] mp 98 °C).

IR (KBr): 3160, 2929, 1603, 1525, 1363, 1267, 849 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 8.1 Hz, 1 H), 7.65 (s, 1 H) 7.64 (s, 1 H), 7.60–7.53 (m, 1 H), 4.72 (s, 1 H), 3.79 (s, 4 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 162.43, 148.24, 132.93, 130.58, 130.47, 127.41, 124.09, 50.76.

2-(4-Chlorophenyl)imidazoline
Yield: 99%; mp 188 °C (Lit.[11] mp 188 °C).

IR (KBr): 3108, 2922, 1601, 1465, 1270, 837, 728 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.5 Hz, 2 H), 7.38 (d, *J* = 8.5 Hz, 2 H), 4.73 (s, 1 H), 3.77 (s, 4 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 163.73, 136.63, 129.01, 128.69, 128.31.

HRMS (ESI): *m*/*z* calcd for $C_9H_{10}ClN_2$ (M + H): 181.05270; found: 181.05246.

2-(3-Chlorophenyl)imidazoline
Yield: 98%; mp 136–138 °C (Lit.[9] mp 136–137 °C).

IR (KBr): 3148, 2928, 1604, 1273, 979, 758, 707 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.79 (s, 1 H), 7.65 (d, *J* = 7.7 Hz, 1 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 7.34 (t, *J* = 7.9 Hz, 1 H), 4.75 (s, 1 H), 3.80 (s, 4 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 163.58, 134.48, 132.30, 130.59, 129.72, 127.24, 125.07, 50.45.

2-(2-Chlorophenyl)imidazoline
Yield: 89%; mp 64 °C (Lit.[9] mp 69–70 °C).

IR (KBr): 3139, 2933, 1612, 1502, 1278, 980, 766 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.79 (dd, *J* = 7.6, 1.8 Hz, 1 H), 7.40 (dd, *J* = 8.0, 1.1 Hz, 1 H), 7.35 (td, *J* = 7.8, 1.8 Hz, 1 H), 7.30 (td, *J* = 7.5, 1.2 Hz, 1 H), 5.20 (s, 1 H), 3.94 (s, 2 H), 3.66 (s, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 163.54, 131.90, 131.32, 131.02, 130.49, 130.16, 126.94.

2-(2,4-Dichlorophenyl)imidazoline
Yield: 88%; mp 98–100 °C (Lit.[9] mp 111–112 °C).

IR (KBr): 3134, 2923, 1606, 1504, 1051, 978, 800 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.4 Hz, 1 H), 7.42 (d, *J* = 2.0 Hz, 1 H), 7.29 (dd, *J* = 8.4, 2.0 Hz, 1 H), 5.16 (s, 1 H), 3.79 (s, 4 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 162.59, 136.40, 132.65, 132.22, 129.99, 128.94, 127.32, 50.44.

2-(4-Methylphenyl)imidazoline
Yield: 94%; mp 178–180 °C (Lit.[8] mp 181 °C).

IR (KBr): 3136, 2925, 1600, 1494, 1271, 985, 827 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.1 Hz, 2 H), 7.21 (d, *J* = 7.9 Hz, 2 H), 3.77 (s, 4 H), 2.38 (s, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 164.01, 140.27, 129.18, 128.36, 127.49, 49.97, 21.41.

2-(4-Methoxyphenyl) imidazoline
Yield: 91%; mp 136–138 °C (Lit.[5h] mp 136–138 °C).

IR (KBr): 3128, 2859, 1607, 1492, 1252, 1029, 839 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.9 Hz, 2 H), 6.91 (d, *J* = 8.9 Hz, 2 H), 4.72 (s, 1 H), 3.84 (s, 4 H), 3.77 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.36, 161.44, 128.52, 123.03, 113.72, 55.32, 50.55.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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