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An efficient and one-pot synthesis of imidazolines and benzimidazoles via anaerobic oxidation of carbon–nitrogen bonds in water

Pranjal Gogoi and Dilip Konwar*

Synthetic Organic Chemistry Division, Regional Research Laboratory, Jorhat 785006, Assam, India

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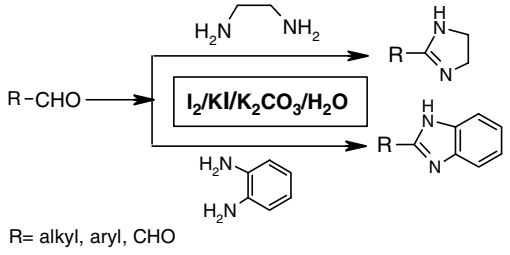
Abstract—The system, $I_2/KI/K_2CO_3/H_2O$, oxidizes carbon–nitrogen bonds for the synthesis of imidazolines and benzimidazoles from aldehydes and diamines under anaerobic conditions in water at 90 °C with excellent yields. The process is green, mild and inexpensive.

The development of simple, efficient and environmentally benign chemical processes or methodologies for widely used organic compounds from readily available reagents is one of the major challenges for chemists in organic synthesis. The importance of imidazoline and benzimidazole units arises, because they are found in many biologically active compounds.[1] In organic synthesis, imidazoline units are also used as synthetic intermediates,[2] chiral auxiliaries,[3] chiral catalysts[4] and ligands for asymmetric catalysis.[5] In addition, the benzimidazole moiety is found in various synthetic pharmaceuticals displaying a broad spectrum of biological activity including anti-ulcer, anti-tumour and anti-viral effects.[6] A number of methods have been reported for the synthesis of imidazolines and benzimidazoles, which include conversion of esters using an aluminium reagent,[7a] the reaction between *N*-ethoxycarbonylthioamides with 1,2-diamines,[7b] and the reaction of aldehydes with 1,2-diamines followed by *N*-halosuccinimides (X = Cl, Br, I).[7c] Recently, several methods have been developed, where azalactones,[8a] 2-aryl-1,1-dibromoethanes,[8b] nitriles[8c] and amino amides[8d] are used as starting materials for this synthesis. However, many of the synthetic protocols reported so far suffer from disadvantages, such as needing anhydrous conditions,[8a] use of organic solvents,[7,8] harsh reaction conditions,[7a] prolonged reaction times,[7c] use of metals and expensive reagents,[7a] etc. Therefore, the development of a cost effective, safe and environment friendly reagent system is desirable.

In recent years, I_2 has been used extensively as a synthetic reagent due to its inherent properties of low toxicity, electrophilicity and easy handling.[9] Recently, we described the Brønsted acid catalyzed oxidation of alcohols to aldehydes and ketones in the presence of DMSO, where the catalyst, HI, was generated via a redox process involving N_2H_4 and I_2.[10a] We have also reported the use of I_2 for the deprotection of ketoximes and aldoximes/imines and for the oxidation of alcohols to aldehydes and ketones in water.[10b] Now we report a practical, inexpensive and green method for the synthesis of imidazolines and benzimidazoles in water.

In a typical procedure, aldehyde (1.0 mmol) and diamine (1.2 mmol) in water (10 ml), were stirred for



Scheme 1. Synthesis of imidazolines and benzimidazoles.

Keywords: Oxidation; Iodine and potassium iodide in water; Imidazoline; Benzimidazole; Water media.
* Corresponding author. Tel.: +91 0376 237009; fax: +91 0376 3370011; e-mail: dkonwar@yahoo.co.uk

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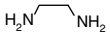
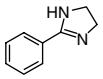
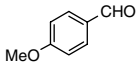
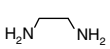
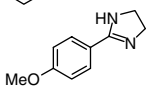
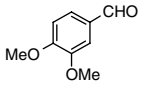
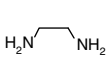
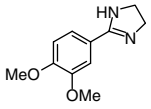
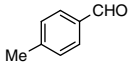
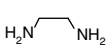
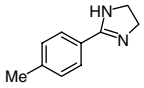
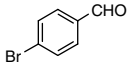
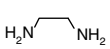
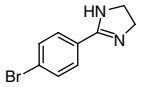
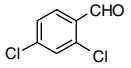
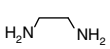
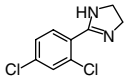
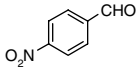
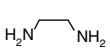
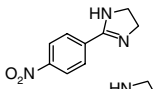
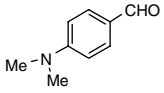
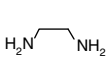
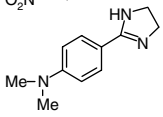
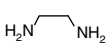
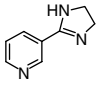
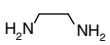
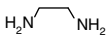
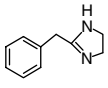
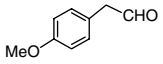
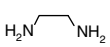
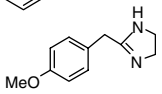
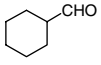
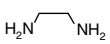
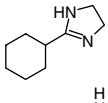
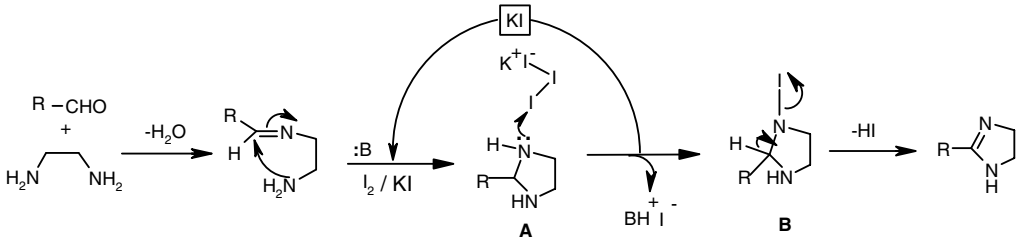
Table 1. Synthesis of imidazolines and benzimidazoles from aldehydes and diamines

Entry	Aldehyde	Diamine	Product	Time (min)	Yield (%)	Physical state mp (°C) (mp lit.)
1				30	90	98–101 (101[16])
2				30	95	140 (137–139[7b])
3				30	95	129–131
4				30	88	180 (181.5–183[7b])
5				30	85	242–246
6				35	80	105–108
7				35	80	231
8				30	80	258–260
9				45	75	102–106 (105–107[16])
10				45	75	178 (178–180[7a])
11				30	80	Oil[8b]
12				30	85	104–106 (104–105[8b])
13				30	84	132 (129–132[7a])
14				45	60	287 (289–291[17])
15				30	75	67–70
16				45	75	295 (290–293[18])
17				45	78	223–226 (226–227[7b])
18				45	75	277 (275–276[7b])
19				50	65	216–219 (218–220[18])
20				50	65	330 (332–334[7b])



Scheme 2. Possible mechanism and tentative intermediates in the synthesis of imidazolines and benzimidazoles.

20 min, potassium carbonate (1.5 mmol), iodine (1 mmol) and potassium iodide (25 mol %) were then added consecutively and the mixture kept at 90 °C with stirring for 30–50 min. After work-up, the corresponding imidazoline or benzimidazole was obtained in good to excellent yield (Scheme 1). The condensation of aldehydes with diamines occurs without any catalyst,[11] and the addition of molecular iodine as an oxidant in the presence of potassium iodide and base, smoothly oxidized the condensed products of aldehydes and diamines to imidazolines/benzimidazoles. It was found that 1.5 equiv of base, potassium carbonate and 25 mol % of KI were optimum for this reaction.

To generalize our reagent system, we synthesized several imidazolines and benzimidazoles under the optimized reaction conditions (Table 1).[12,13] No iodinated or over-oxidized product (i.e., imidazole) were found in the reaction mixtures.[8b] During the oxidation step, other functionalities such as methoxy, chloro, bromo, alkyl and aryl present in the substrates survived. Aromatic aldehydes, having different substituents such as methoxy, chloro, bromo, methyl, etc. were converted to the corresponding imidazolines and benzimidazoles in high yields (Table 1). Nicotinaldehyde and 2-thiophenecarboxaldehyde also gave the desired products in high yields. Straight chain as well as cyclic aliphatic aldehydes were transformed to the respective imidazolines with good yields. For the synthesis of benzimidazoles from aldehydes, we used *o*-phenylenediamine as a starting material with several aromatic aldehydes (Table 1). The yields of the reactions were dependent on the substituents present on the substrates and on steric factors. Reactions with substrates having electron-withdrawing groups such as chloro, bromo, etc. proceeded at faster rates then those with electron-donating groups such as Me, *N*,*N*′-dimethylamino, etc., whilst *ortho*-substituted aldehydes gave products in lower yields than *m*- and *p*-substituted examples.

Regarding the mechanism of the oxidation step, it is proposed that the imidazolidine, **A** reacts with KI_3 (generated in situ from I_2 and KI),[14] in the presence of base to form an intermediate **B**, which eliminates HI to generate the imidazoline.[15] Finally the generated acid (HI) is scavenged by the inorganic base to produce KI in water (Scheme 2).

In conclusion, the present synthetic method is a simple, efficient, inexpensive and green synthesis of biologically active imidazolines and benzimidazoles via an oxidation process with iodine, potassium iodide and potassium carbonate in water. The advantages of the present reaction are the elimination of metals, organic solvents and toxic reagents, operational simplicity and high yields of products.

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12. General experimental procedure for the synthesis of imidazolines/benzimidazoles: A solution of diamine (1.0 mmol) and aldehyde (1.0 mmol) in water (10 ml) was stirred at room temperature for 20 min, then potassium carbonate (1.5 mmol) was added and the mixture stirred for another 10 min. An aqueous solution of KI (0.25 mmol) and I_2 (0.06 g, 0.25 mmol) in water (5 ml) was added, and then further I_2 (0.75 mmol) was added portionwise over 5 min, and the mixture was heated at 90 °C with stirring for the stipulated time (Table 1). Sodium thiosulfate solution (10 ml; 5%) was added and the product was extracted with ethyl acetate (15 ml × 3). The combined ethyl acetate layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product, which was purified by crystallization or column chromatography (silica gel) using hexane and ethyl acetate as eluent.
13. Unknown compounds or compounds for which incomplete physical data were reported in the literature were characterized by FTIR, NMR (^{1}H, ^{13}C) and elemental analysis. Selected data:
    2-(3,4-Dimethoxyphenyl)imidazoline (entry 3). Solid; mp 129 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.84–7.46 (m, 3H), 3.93 (s, 3H), 3.92 (s, 3H), 3.78 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 50.0 (br), 56.2, 56.3, 111.2, 111.5, 120.9, 123.4, 126.3, 148.9, 151.4, 164.5; FTIR (KBr): 3178 (NH), 2962 and 2918 (CH), 1615.3 (C=N) cm^{-1}; Anal. Calcd for $C_{11}H_{14}N_2O_2$ (206.244): C, 64.06; H, 6.84; N, 13.58. Found: C, 64.40; H, 6.84; N, 13.54; HRMS calcd for $C_{11}H_{14}N_2O_2$ (M^+) 206.244, found 206.267.
    2-(4-Bromophenyl)imidazoline (entry 5). Solid; mp 242–246 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.70–7.80 (m, 4H), 3.90 (s, 4H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 47.4 (br), 96.3, 126.3, 130.4, 132.5, 165.0; FTIR (KBr): 3183 (NH), 2962 and 2944.5 (CH), 1609.94 (C=N) cm^{-1}; Anal. Calcd for $C_9H_9N_2Br$ (225.088): C, 48.02; H, 4.03; N, 12.45. Found: C, 48.44; H, 4.06; N, 12.49; HRMS calcd for $C_9H_9N_2Br$ (M^+) 225.088, found 225.051.
    2-(2,4-Dichlorophenyl)imidazoline (entry 6). Solid; mp 105–108 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26–7.76 (m, 3H), 4.30 (br, 1H), 3.79 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 50.72 (br), 127.77, 129.22, 130.41, 132.64, 133.03, 136.86, 163.02; FTIR (KBr): 3132 (NH), 2930 (CH), 1608 (C=N) cm^{-1}. Anal. Calcd for $C_9H_8N_2Cl_2$ (215.082): C, 50.26; H, 3.75; N, 13.02. Found: C, 50.26; H, 3.76; N, 13.02; HRMS calcd for $C_9H_8N_2Cl_2$ (M^+) 215.082, found 215.123.
    2-(4-Nitrophenyl)imidazoline (entry 7). Solid; mp 231 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.04 (d, 2H, $J = 8.5$ Hz), 7.83 (d, 2H, $J = 8.5$ Hz), 3.59 (s, 4H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 49.80 (br), 123.56, 125.1, 128.6, 136.5, 148.5, 164.2; FTIR (KBr): 3188 (NH), 2945 (CH), 1683 (C=N) cm^{-1}. Anal. Calcd for $C_9H_9N_3O_2$ (191.189): C, 56.54; H, 4.74; N, 21.98. Found: C, 56.57; H, 4.74; N, 21.99; HRMS calcd for $C_9H_9N_3O_2$ (M^+) 191.189, found 191.172.
    2-(4-*N*,*N*′-Dimethylaminophenyl)imidazoline (entry 8). Solid; mp 258–260 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.82 (d, 2H, $J = 8.3$ Hz), 6.94 (d, 2H, $J = 8.3$ Hz), 4.75 (s, 4H), 3.00 (s, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 44.66 (br), 107.45, 111.53, 126.30, 131.00, 154.54, 164.42; FTIR (KBr): 3178 (NH), 2962 and 2918 (CH), 1615 (C=N) cm^{-1}; Anal. Calcd for $C_{11}H_{15}N_3$ (189.26): C, 69.81; H, 8.00; N, 22.03. Found: C, 69.91; H, 7.96; N, 22.01; HRMS calcd for $C_{11}H_{15}N_3$ (M^+) 189.260, found 189.253.
    2-(Nonyl)imidazoline (entry 15). Solid; mp 67–70 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.80 (br, 1H), 3.56 (s, 4H), 0.85–2.24 (m, 19H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.51, 23.06, 27.09, 29.55, 29.67, 29.75, 29.83, 29.90, 32.27, 50.22 (br), 168.45; FTIR (KBr): 3189 (NH), 2948 and 2925 (CH), 1613 (C=N) cm^{-1}; Anal. Calcd for $C_{12}H_{24}N_2$ (196.335): C, 73.41; H, 12.32; N, 14.27. Found: C, 73.35; H, 12.33; N, 14.27; HRMS calcd for $C_{12}H_{24}N_2$ (M^+) 196.335, found 196.324.
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