An Efficient Preparation of 2-Imidazolines and Imidazoles from Aldehydes with Molecular Iodine and (Diacetoxyiodo)benzene

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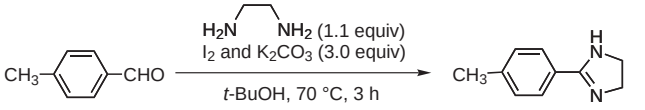
Abstract: 2-Imidazolines were easily prepared in quite good yields from the reaction of aldehydes and ethylenediamine with molecular iodine in the presence of potassium carbonate. Moreover, 2-imidazolines obtained were smoothly oxidized to the corresponding imidazoles in good yields using (diacetoxyiodo)benzene at room temperature.

Key words: 2-imidazoline, imidazole, iodine, (diacetoxyiodo)benzene, aldehyde, ethylenediamine

Synthetic study of 2-imidazoline units and imidazole units is very important due to their potent biological activity[1] and synthetic utility.[2] To date, there are several synthetic methods for 2-imidazolines starting from mainly nitriles and esters.[3] Recently, Kita et al. reported an efficient one-pot preparation of 2-imidazolines from aldehydes and ethylenediamine with NBS.[4] Once 2-imidazolines are formed, they can be smoothly oxidized to the corresponding imidazoles by oxidants such as MnO_2,[5a] Pd/C,[5b] $KMnO_4$,[5c] trichloroisocyanuric acid,[5d] $(COCl)_2$–DMSO,[5e] and IBX,[5f] etc. However, there are still several drawbacks to these methods, i.e., preparation of 2-imidazolines and imidazoles requires toxic or explosive oxidant, or multistep operation. Recently, synthetic use of hypervalent iodines for organic synthesis has been investigated widely because of their efficient oxidizing ability and less toxicity.[6] Especially, (diacetoxyiodo)benzene (DIB), iodosylbenzene, and [hydroxy(tosyloxy)iodo]benzene (HTIB) are the most popular and useful trivalent iodine reagents for organic synthesis.[7]

Here, as a part of our basic study of molecular iodine for organic synthesis,[8] we would like to report a useful oxidative conversion of aldehydes to 2-imidazolines with ethylenediamine and iodine, and then to imidazoles with DIB. Thus, the addition of molecular iodine to a mixture of *p*-tolualdehyde and ethylenediamine in the presence of K_2CO_3 provided the corresponding 2-(4-methylphenyl)imidazoline, and the use of 1.25 equivalents of molecular iodine gave the product quantitatively as shown in Table 1 (entry 3).[9] According to our previous reported reaction conditions using molecular iodine,[8b] *t*-BuOH was used as a solvent in the present reaction. ICl is also effective, but molecular iodine is much more efficient in view of the operational utility of the reagent and the yield obtained (entry 5). The same treatment of *p*-tolualdehyde with DIB, instead of molecular iodine, gave a complicated reaction mixture, and 2-(4-methylphenyl)imidazoline was not formed at all. Based on these results, various aldehydes were treated with ethylenediamine and molecular iodine under the same conditions to provide the corresponding 2-substituted imidazolines in quite good yields, as shown in Table 2. Thus, aromatic aldehydes bearing electron-donating substituents and electron-withdrawing substituents can be converted to the corresponding 2-arylimidazolines in quite good yields. However, the reaction of aliphatic aldehyde under the same conditions gave the corresponding 2-alkylimidazoline in moderate yields (entries 8, 9).

Table 1 Formation of 2-(*p*-Tolyl)imidazoline from *p*-Tolualdehyde with Ethylenediamine and Iodine



Entry	I_2 (equiv)	Yield (%)
1	0.75	82
2	1.00	89
3	1.25	100
4	1.50	100
5	2.5[a]	83

[a] ICl was used in place of I_2.

Then, the oxidation of 2-(4-methylphenyl)imidazoline to 2-(4-methylphenyl)imidazole in the presence of K_2CO_3, using less-toxic iodine reagents such as molecular iodine or hypervalent iodine reagents, was carried out as shown in Table 3.[10] Though it is well-known that molecular iodine has moderate oxidizing ability, unfortunately 2-(4-methylphenyl)imidazoline could not be oxidized by iodine under any conditions. However, hypervalent iodine reagents such as DIB, iodosylbenzene, and HTIB oxidize it to 2-(4-methylphenyl)imidazole in DMSO at room temperature, and DIB showed the most effective reactivity among them, to give the product in good yield (entry 5).

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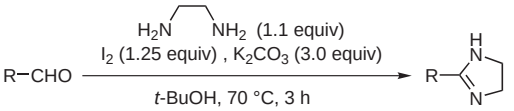
Table 2 Preparation of 2-Substituted Imidazolines from Aldehydes with Ethylenediamine and Iodine



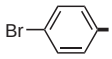
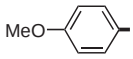
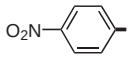
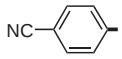
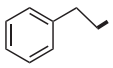
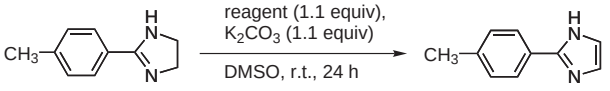
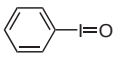
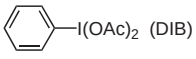
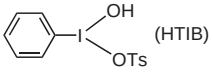
Entry	R =	Yield (%)
1		100
2		97
3		100
4		99
5		98
6		99
7		94
8		53
9		50

Table 3 Oxidation of 2-(*p*-Tolyl)imidazoline to 2-(*p*-Tolyl)imidazole with DIB

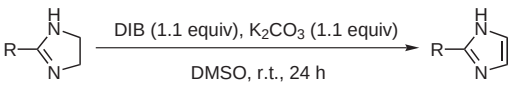


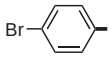
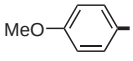
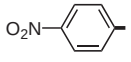
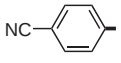
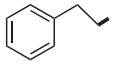
Entry	Reagent	Yield (%)
1	I_2	0
2	I_2–H_2O_2[a]	0
3	KI–H_2O_2[a]	0
4		36
5	 (DIB)	81
6	 (HTIB)	23

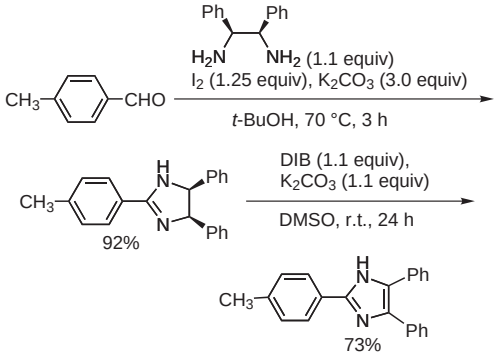
[a] H_2O_2 (3.0 equiv) was added.

Acetonitrile and DMF, instead of DMSO, also gave 2-(4-methylphenyl)imidazole under the same conditions; however, the yield was much decreased. Based on these results, various 2-substituted imidazolines were efficiently oxidized to the corresponding 2-substituted imidazoles in good yields as shown in Table 4. However, the same treatment of 2-alkylimidazoline with DIB gave the corresponding 2-alkylimidazole in low yields (entries 8, 9). Finally, the same treatment of *p*-tolualdehyde with (*R*,*R*)-(+)-diphenylethylenediamine, instead of ethylenediamine, provided the corresponding (*R*,*R*)-2-(*p*-tolyl)-3,4-diphenylimidazoline in 92% yield, and the oxidation with DIB produced the corresponding 2-(*p*-tolyl)-3,4-diphenylimidazole in 73% yield (Scheme 1). A plausible reaction mechanism for imidazolines and imidazoles is shown in Scheme 2.

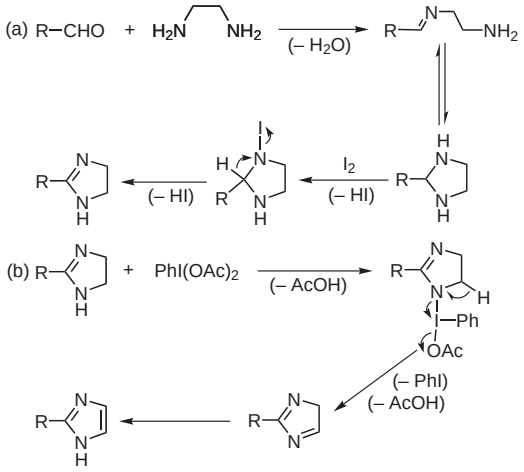
Table 4 Oxidation of 2-Substituted Imidazolines to 2-Substituted Imidazoles with DIB



Entry	R =	Yield (%)
1		75
2		83
3		76
4		73
5		79
6		70
7		70
8		38
9		41



Scheme 1



Scheme 2 Plausible reaction mechanisms for imidazoline (a) and imidazole (b)

In summary, 2-imidazolines could be easily obtained in quite good yields by the reaction of aldehydes and ethylenediamine with molecular iodine in the presence of potassium carbonate under warming conditions. Then, 2-imidazolines obtained could be smoothly oxidized to the corresponding imidazoles in good yields using (diacetoxyiodo)benzene at room temperature. Both reactions proceed under environmentally benign conditions, i.e., without using any toxic reagents. Further synthetic study of the present reactions is underway in this laboratory.

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References and Notes

(1) (a) Grimmett, M. R. *Comprehensive Heterocyclic Chemistry*, Vol. 5; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon: Oxford, **1984**, 345–498. (b) Grimmett, M. R. *Comprehensive Heterocyclic Chemistry II*, Vol. 3; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Elsevier Science: Oxford, **1996**, 77–220. (c) *The Pharmacological Basis of Therapeutics*, 10th ed.; Gilman, A. G.; Goodman, L. S., Eds.; Macmillan: New York, **2001**. (d) Prisinano, T.; Law, H.; Dukat, M.; Slassi, A.; MaClean, N.; Demchyshyn, L.; Glennon, R. A. *Bioorg. Med. Chem.* **2001**, *9*, 613.

(2) For examples see: (a) Jones, R. C. F.; Nichols, J. R. *Tetrahedron Lett.* **1990**, *31*, 1771. (b) Langlois, Y.; Dalko, P. I. *J. Org. Chem.* **1998**, *63*, 8107. (c) Menges, F.; Neuburger, M.; Pfaltz, A. *Org. Lett.* **2002**, *4*, 4713. (d) Meiere, S. H.; Valahovic, M. T.; Harman, W. D. *J. Am. Chem. Soc.* **2002**, *124*, 15099. (e) Bhor, S.; Anilkumar, G.; Tse, M. K.; Klawonn, M.; Döbler, C.; Bitterlich, B.; Grotevendt, A.; Beller, M. *Org. Lett.* **2005**, *7*, 3393.

(3) For examples see: (a) Ferm, R. J.; Riebsomer, J. L. *Chem. Rev.* **1954**, *54*, 593. (b) Hughey, J. L. I. V.; Knapp, S.; Schugar, H. *Synthesis* **1980**, 489. (c) Quaglia, W.; Bousquet, P.; Pigini, M.; Carotti, A.; Carrieri, A.; Dontenwill, M.; Gentili, F.; Giannella, M.; Maranca, F.; Piergentili, A.; Brasili, L. *J. Med. Chem.* **1999**, *42*, 2737. (d) Anastassiadou, M.; Baziard-Mouysset, G.; Payard, M. *Synthesis* **2000**, 1814. (e) Neef, G.; Eder, U.; Sauer, G. *J. Org. Chem.* **1981**, *46*, 2824. (f) Mitchell, J. M.; Finney, N. S. *Tetrahedron Lett.* **2000**, *41*, 8431. (g) Peddibhotla, S.; Tepe, J. J. *Synthesis* **2003**, 1433. (h) You, S.; Kelly, J. W. *Org. Lett.* **2004**, *6*, 1681.

(4) Fujioka, H.; Murai, K.; Ohba, Y.; Hiramatsu, A.; Kita, Y. *Tetrahedron Lett.* **2005**, *46*, 2197.

(5) (a) Martin, P. K.; Matthews, H. R.; Rapoport, H.; Thyagarajan, G. *J. Org. Chem.* **1968**, *33*, 3758. (b) Amemiya, Y.; Miller, D. D.; Hsu, F. L. *Synth. Commun.* **1990**, *20*, 2483. (c) Mohammadpoor-Baltork, I.; Zolfigol, M. A.; Abdollahi-Alibeik, M. *Tetrahedron Lett.* **2004**, *45*, 8687; and references cited therein. (d) Mohammadpoor-Baltork, I.; Zolfigol, M. A.; Abdollahi-Alibeik, M. *Synlett* **2004**, 2803. (e) Huh, D. H.; Ryu, H.; Kim, Y. G. *Tetrahedron* **2004**, *60*, 9857. (f) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *Angew. Chem. Int. Ed.* **2003**, *42*, 4077.

(6) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: San Diego, **1997**.

(7) Reviews: (a) Ochiai, M. *Rev. Heteroat. Chem.* **1989**, *2*, 92. (b) Moriarty, R. M.; Vaid, R. K. *Synthesis* **1990**, 431. (c) Moriarty, R. M.; Vaid, R. K.; Koser, G. F. *Synlett* **1990**, 365. (d) Stang, P. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 274. (e) Prakash, O.; Saini, N.; Sharma, P. K. *Synlett* **1994**, 221. (f) Kitamura, T. *Yuki Gosei Kagaku Kyokaishi* **1995**, *53*, 893. (g) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123. (h) Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757. (i) Kita, Y.; Takada, T.; Tohma, H. *Pure Appl. Chem.* **1996**, *68*, 627. (j) Togo, H.; Hoshina, Y.; Nogami, G.; Yokoyama, M. *Yuki Gosei Kagaku Kyokaishi* **1997**, *55*, 90. (k) Varvoglis, A. *Tetrahedron* **1997**, *53*, 1179. (l) Zhdankin, V. V. *Rev. Heteroat. Chem.* **1997**, *17*, 133. (m) Muraki, T.; Togo, H.; Yokoyama, M. *Rev. Heteroat. Chem.* **1997**, *17*, 213. (n) Kitamura, T.; Fujiwara, Y. *Org. Prep. Proced. Int.* **1997**, *29*, 409. (o) Varvoglis, A.; Spyroudis, S. *Synlett* **1998**, 221. (p) Zhdankin, V. V.; Stang, P. J. *Tetrahedron* **1998**, *54*, 10927. (q) Moriarty, R. M.; Prakash, O. *Adv. Heterocycl. Chem.* **1998**, *69*, 1. (r) Kita, Y.; Egi, M.; Takada, T.; Tohma, H. *Synthesis* **1999**, 885. (s) Wirth, T.; Hirt, U. H. *Synthesis* **1999**, 1271. (t) Ochiai, M.; Kitagawa, Y. *Yuki Gosei Kagaku Kyokaishi* **2000**, *58*, 1048. (u) Togo, H.; Katohgi, M. *Synlett* **2001**, 565. (v) Wirth, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 2812. (w) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (x) Togo, H.; Sakuratani, K. *Synlett* **2002**, 1966. (y) Tohma, H.; Kita, Y. *Adv. Synth. Catal.* **2004**, *346*, 111. (z) Tohma, H.; Kita, Y. *Yuki Gosei Kagaku Kyokaishi* **2004**, *62*, 116.

(8) (a) Mori, N.; Togo, H. *Synlett* **2004**, 880. (b) Mori, N.; Togo, H. *Tetrahedron* **2005**, *61*, 5915. (c) Mori, N.; Togo, H. *Synlett* **2005**, 1456.

(9) **Typical Procedure for Preparation of 2-Imidazolines from Aldehydes:** To a solution of *p*-tolualdehyde (120.2 mg, 1 mmol) in *t*-BuOH (10 mL) was added ethylenediamine (66.1 mg, 1.1 mmol). The obtained mixture was stirred at r.t. under an argon atmosphere for 30 min, and then K_2CO_3 (414.6 mg, 3 mmol) and I_2 (317.3 mg, 1.25 mmol) were added to the mixture and stirred at 70 °C. After 3 h, the mixture was quenched with sat. aq Na_2SO_3 until the

iodine color almost disappeared, and was extracted with $CHCl_3$. The organic layer was washed with sat. aq $NaHCO_3$ and brine, and dried over Na_2SO_4. After filtration, the mixture was evaporated in vacuo to provide 160.2 mg of 2-(4-methylphenyl)imidazoline in 100% yield in an almost-pure state. Mp 181–182 °C (lit.[11] mp 181 °C). IR (KBr): 3140, 2925, 1600, 1495, 985, 830 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3 H), 3.77 (s, 4 H), 7.21 (d, *J* = 8.3 Hz, 2 H), 7.67 (d, *J* = 8.3 Hz, 2 H).

(10) **Typical Procedure for Oxidation of 2-Imidazolines to Imidazoles:** To a mixture of 2-(4-methylphenyl)imidazoline (160.2 mg, 1 mmol) and K_2CO_3 (152.0 mg, 1.1 mmol) in DMSO (10 mL) was added DIB (354.3 mg, 1.1 mmol). Then the mixture was stirred for 24 h at r.t. under an argon atmosphere. After the reaction, the reaction mixture was diluted with sat. aq $NaHCO_3$ and EtOAc, and was stirred for 5 min. The mixture was extracted with EtOAc and the organic layer was dried over Na_2SO_4. After filtration, the mixture was evaporated in vacuo. The residue was chromatographed on neutral silica gel (EtOAc–MeOH, 30:1) to give 128.1 mg of 2-(4-methylphenyl)imidazole in 81% yield in an almost-pure state. Mp 217–218 °C (lit.[5d] mp 218–220 °C). IR (KBr): 3460, 1515, 1445, 1100, 820, 730 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 2.31 (s, 3 H), 6.97 (br s, 1 H), 7.19 (br s, 1 H), 7.21 (d, *J* = 8.2 Hz, 2 H), 7.81 (d, *J* = 8.2 Hz, 2 H), 12.38 (s, 1 H).

(11) Levesque, G. *Synthesis* **1981**, 963.