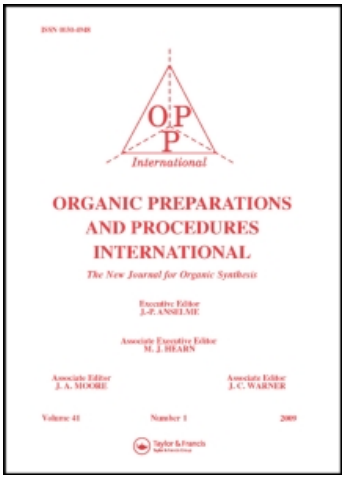

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IODINE AS AN EFFICIENT CATALYST FOR THE SYNTHESIS OF BENZIMIDAZOLES AND IMIDAZOLINES FROM PRIMARY ALCOHOLS AND DIAMINES

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IODINE AS AN EFFICIENT CATALYST FOR THE SYNTHESIS OF BENZIMIDAZOLES AND IMIDAZOLINES FROM PRIMARY ALCOHOLS AND DIAMINES

Submitted by (03/15/07)

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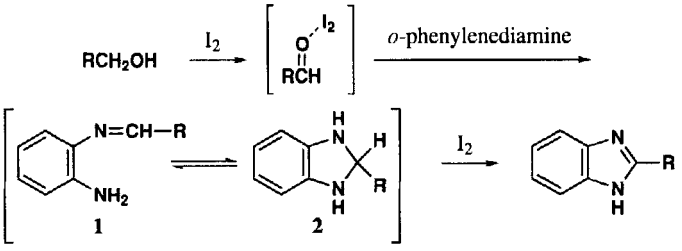
Benzimidazoles and imidazolines are very useful intermediates for the development of molecules of pharmaceutical or biological interest. Substituted benzimidazole derivatives have found applications in diverse therapeutic areas including antiulcers, antihypertensives, antivirals, antifungals, anticancers, and antihistaminics to name just a few.[1] In addition, imidazoline units are also used as synthetic intermediates, chiral auxiliaries, chiral catalysts and ligands for asymmetric catalysis.[2] Due to their wide range of pharmacological activity, industrial and synthetic applications, a number of methods have been reported for the synthesis of benzimidazoles and imidazolines, which include preparation from esters using aluminium organic reagents as the catalyst,[3a] the reaction between *N*-ethoxycarbonylthioamides with 1,2-diamines,[3b] and the reaction of aldehydes with 1,2-diamines followed by *N*-halosuccinimides (X = Cl, Br, I).[3c] Recently, several methods have been developed, where azalactones,[4a] 2-aryl-1,1-dibromoethanes,[4b] nitriles[4c] and amino amides[4d] have been used as starting materials for this synthesis. However, many of the synthetic protocols suffer from disadvantages, such as requring anhydrous[4a] or harsh reaction conditions,[3a] prolonged reaction times,[3c] use of metals and expensive reagents,[3a] etc.

Recently, molecular iodine[5] has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations to afford the corresponding

products in excellent yields and high selectivity. The mild Lewis acidity associated with iodine enhances its usage in organic synthesis to realize several organic transformations using stoichiometric level to catalytic amounts.[6] Ishihara and Togo[7a] have previously described the synthesis imidazolines from aldehydes and ethylenediamine using I_2 and K_2CO_3 in *t* –BuOH. Gogoi and Konwar[7b] also reported a new method for the synthesis of imidazolines and benzimidazoles from aldehydes and diamines in the system of $I_2/KI/K_2CO_3/H_2O$. To the best of our knowledge, reports on the direct oxidative conversion of primary alcohols to the benzimidazoles or imidazolines with molecular iodine have not appeared. Now we report a facile method for the synthesis benzimidazoles and imidazolines from primary alcohols and diamines using I_2/K_2CO_3 system, in which I_2 serves a dual purpose as an oxidant (*Scheme 1*).



Scheme 1

First, the addition of 3.0 equivalents of molecular iodine and potassium carbonate to a mixture of *o*-chlorobenzyl alcohol and *o*-phenylenediamine provided the corresponding 2-(*o*-chlorophenyl)benzimidazole in 59% yield, and the use of 5.0 equivalents of molecular iodine and potassium carbonate gave the product in a greater yield as shown in *Table 1* (Entry 3). According to Togo's previously reported reaction conditions using molecular iodine,[7a,7c] *t*-BuOH was used as solvent in the present reaction.

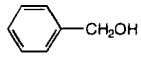
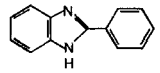
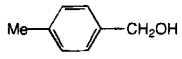
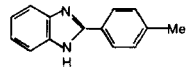
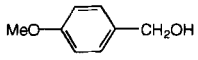
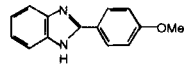
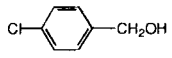
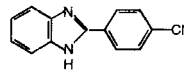
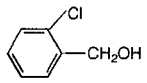
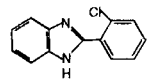
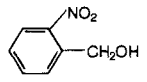
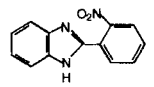
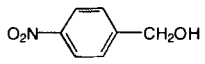
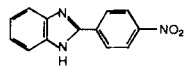
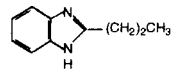
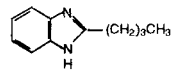
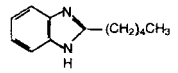
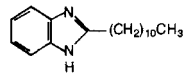
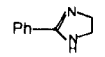
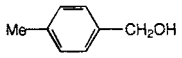
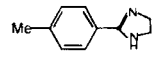
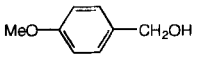
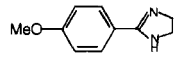
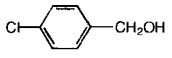
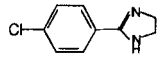
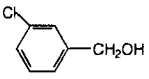
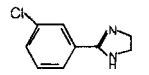
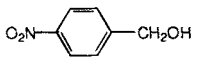
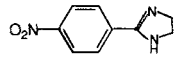
Table 1. Effect of the Ratio of I_2/K_2CO_3 on the Yields of 2-(*o*-Chlorophenyl)benzimidazole

I_2/K_2CO_3 (eq/eq)	3/3	4/4	5/5	6/6	7/7
Yield	59%	71%	86%	87%	86%

Several benzimidazoles and imidazolines were synthesized to explore the scope under the optimized reaction conditions (*Table 2*). *Table 2* shows both electron-deficient and electron-rich benzylic alcohols were converted to the corresponding benzimidazoles and imidazolines in high yields. However, the reaction of aliphatic alcohols under the same conditions gave the corresponding 2-alkylbenzimidazoles in moderate yields (*Entries 8, 9*), and the yields of benzimidazoles were higher than that of imidazolines.

A plausible reaction mechanism for benzimidazoles is shown in *Scheme 1*. First, the primary alcohols are oxidized to the corresponding aldehydes by iodine in *t*-BuOH.[7c] Once aldehydes are formed, the amino group of *o*-phenylenediamine attacks the carbonyl group of the

Table 2. I_2/K_2CO_3 Catalyzed Synthesis of Benzimidazoles and Imidazolines in *t*-BuOH

Entry	Alcohol	Product	Yield (%)	mp. (mp. *lit.*) (°C)
1			95	291-292 (292[8a])
2			94	268-271 (270[8a])
3			85	224-225 (226[8a])
4			85	291-292 (290[8a])
5			86	233-236 (234[8a])
6			86	209-211 (210[8a])
7			90	314-316 (316[8a])
8	*n*-BuOH		63	161-163 (162[8a])
9	$CH_3(CH_2)_3CH_2OH$		62	157-158 (155-155.5[8b])
10	$CH_3(CH_2)_4CH_2OH$		57	161-163 (163-163.5[8b])
11	$CH_3(CH_2)_{10}CH_2OH$		44	105-107 (107.5[8b])
12	$PhCH_2OH$		73	97-99 (100-101[8c])
13			75	179-180 (177-179[8c])
14			70	138-140 (137-139[8c])
15			71	184-186 (186-188[8c])
16			70	134-136 (133-135[8c])
17			71	230-232 (231[7b])

aldehydes, which are activated by iodine,[9a] giving the intermediate Schiff's bases **1**. The Schiff's bases **1** exist in equilibrium with the cyclic dihydrobenzimidazoles **2** that were then oxidized to benzimidazoles by iodine.[9b]

In conclusion, we have developed a simple, inexpensive and efficient method for the preparation benzimidazoles and imidazolines from primary alcohols and diamines in the presence of molecular iodine and potassium carbonate. Further studies on the synthetic applications are now in progress.

EXPERIMENTAL SECTION

IR spectra were recorded on a Bomem MB154S infrared analyzer. UV-Vis spectra were obtained with a UV-1601 apparatus. ^{1}H NMR spectra were recorded on Bruker Advance DMX500. Mass spectra were recorded on a Saturn 2000GC/MS instrument. Primary alcohols were commercially obtained from ARCOS Co. All chemicals were of analytical grade.

Typical Procedure for the Synthesis of 2-(*o*-Chlorophenyl)benzimidazole.- To a solution of *o*-chlorobenzyl alcohol (143 mg, 1 mmol) in *t*-BuOH (10 mL) were added I_2 (1.27 g, 5 mmol) and K_2CO_3 (691 mg, 5 mmol), the mixture obtained was stirred for 2 h at 50°C, then *o*-phenylenediamine (119 mg, 1.1 mmol) was added to the mixture and stirred at 70°C. After 3 h, the completion of reaction was monitored by TLC (35% EtOAc in petroleum ether), the mixture was treated with aqueous $Na_2S_2O_3$ (5%, 40 mL). A precipitate was immediately formed which was then filtered, washed with water (2 x 10 mL) and dried to yield crude 2-(*o*-chlorophenyl)benzimidazole, which was purified by column chromatography on silica gel (20% EtOAc in petroleum ether) to afford 197 mg (86%) of pure product 2-(*o*-chlorophenyl)benzimidazole, mp. 233-236°C, *lit.*[8a] mp. 234°C; IR (KBr cm^{-1}): 3300-3500 (the broad peak); 1589, 1536, 1443, 1316, 1227, 1051, 745. ^{1}H NMR (500 MHz, DMSO): δ 7.25 (m, 2H), 7.54 (m, 2H), 7.65 (m, 3H), 7.93 (m, 1H), 12.63 (s, 1H).

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