Solvent-Free Chemoselective Synthesis of Some Novel Substituted 2-Arylbenzimidazoles Using Amino Acid-Based Prolinium Nitrate Ionic Liquid as Catalyst

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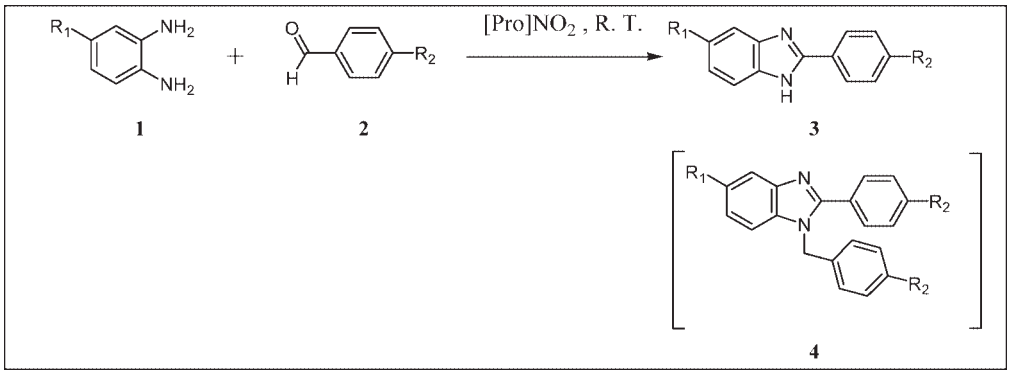
Received February 26, 2008
DOI 10.1002/jhet.35
Published online 11 February 2009 in Wiley InterScience (www.interscience.wiley.com).



A simple and eco-friendly protocol for the synthesis of substituted 2-arylbenzimidazoles is described. In this process, 2-arylbenzimidazoles were prepared in the presence of a newly introduced ionic liquid prolinium nitrate [Pro]NO_3 as catalyst, under solvent-free condition. This process was performed under mild condition without using any oxidant with good to excellent yields and remarkable chemoselectivity in the absence of any byproduct. The ionic liquid can be recovered easily and reused.

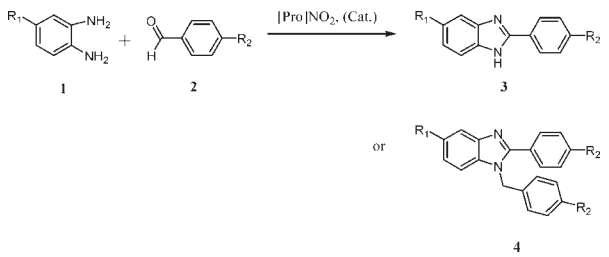
J. Heterocyclic Chem., **46**, 74 (2009).

INTRODUCTION

The benzimidazole ring system is an important pharmacophore in medicinal chemistry and modern drug discovery. Benzimidazole derivatives exhibit activities against several viruses such as influenza [1a], human cytomegalovirus [1b], and HIV [1c]. Benzimidazole and its derivatives have also been known to act as topoisomerase inhibitors [2], selective neuropeptide Y Y 1 receptor antagonists [3], potential antitumor [4] and antimicrobial agents [5], and factor Xa inhibitor [6]. The widespread interest in benzimidazole-containing structures has led to extensive studies toward their synthesis. The most important methodology toward synthesis of benzimidazoles is the oxidative cyclo-dehydrogenation of aniline Schiff bases, which are often generated *in situ* from the coupling reaction between *o*-phenylenediamines and aldehydes. Various oxidants have been examined for this two step process which we hereby refer to some of them such as nitrobenzene (high-boiling oxidant/solvent) [7], 1,4-benzoquinone [8] DDQ [9], tetracyanothylene [10], benzofuroxan [11], MnO_2 [12], $Pb(OAc)_4$ [13], oxone [14], and $NaHSO_3$ [15]. The availability of a vast number of aldehydes has certainly caused this two-step process to be extensively investigated by chemists. However, most of these procedures produce toxic or environmentally harmful byproducts, which often require laborious work-up to remove them from the reaction mixture, and/or suffer from low yields of isolation product. Molecular oxygen as oxidant has also been used but drawbacks such as prolonged reaction times and high temperature make it less useful [16]. In the case of $I_2/KI/K_2CO_3/H_2O$ system, the yields for aldehydes with electron-donating groups were poor [17]. Very recently, iodobenzene diacetate (IBD) as oxidant in dioxane as solvent has led to significant results but the use of dioxane as a toxic solvent is the major limitation for this process from the environmental viewpoint [18]. In another report, application of L-proline in $CHCl_3$ as organocatalyst was presented but this route led to the formation of 1,2-di-substituted benzimidazoles exclusively not the 2-aryl derivatives [19].

The drive to environmentally sustainable, or so-called ''green chemistry,'' has provided one of the greatest challenges for the chemists of today [20a]. One of the major areas of research in this field is using ionic liquids (ILs) as both solvents and catalysts [20b]. There is only one report regarding formation of these compounds using an imidazolium IL (butylimidazolium tetrafluoroborate, ([Hbim]BF_4) as medium. In this process, the yields are good and the reaction times were short, and

Scheme 1



formation of byproducts had a negative effect on the yield [21].

ILs based on amino acids such as proline are one of the most important groups of recently developed ILs referred to as fully green ILs based on natural products. Their importance includes two different aspects. Bio-renewability and economical benefits are the major features of materials of this kind. Moreover, ILs of this type do not show defects such as air- or water-sensitivity of chloroaluminate ILs nor the potential HF releasing of hexafluorophosphate ILs. So, because of these advantages, attempts for the development and introduction of novel ILs based on natural products such as amino acids have been intensively investigated [22]. The main thrust of this work was to provide a new oxidant-free, selective and more sustainable protocol for the synthesis of 2-arylbenzimidazoles.

To the best of our knowledge, benzimidazole derivatives have rarely been synthesized with electron withdrawing substituents such as NO_2 and CO_2H on the fused benzo ring of benzimidazole. So, our other goal was to synthesize such derivatives using 4-nitro-1,2-phenyl-enediamine and 3,4-diaminobenzoic acid as reactant.

RESULTS AND DISCUSSION

During our investigation, at first, we chose *o*-phenylenediamine and 4-chlorobenzaldehyde as model reactants and examined the effect of the amount of prolinium nitrate ([Pro]NO_3) IL as catalyst in the absence of solvent under various temperatures (Scheme 1, Table 1).

To determine the optimum reaction conditions, three moles of phenylenediamines and three moles of 4-chlorobenzaldehyde together with a specified amount of IL were reacted under different temperatures. The results in Table 1 showed some interesting points. First of all, increasing amount of IL did not improve obviously the yield of **3e**. So, the optimum amount of IL was found to be 20% relative to reactants. The second important point which could be elicited evidently from these results is that raising the reaction temperature from r.t. to 60°C did not increase the yield and also did not improve the reaction rates. Moreover, the chemoselectivity decreased and formation of the byproduct **4** was observed in the process. These results indicates that the reaction is better to be carried out at r.t. using 20 mol % amount of IL without solvent to achieve the best results for the preparation of desired product **3** not product **4**.

Then, we continued our study to examine the reusability and recoverability of the catalyst as an additional important factor in the field of ILs. To achieve this, the model reaction of *o*-phenylenediamine (4 mmol) with 4-chlorobenzaldehyde (4 mmol) was carried out in the presence of IL (0.8 mmol). After completion of the reaction, the IL could be recovered as specified in Experimental section. The results of which are given in Table 2. These results showed a good recoverability and reusability for the synthesis of product **3e**. It can clearly be seen that even after four runs, the recovery percentage is high. However, the yield decreased significantly after four runs (Table 2, Run No. 4).

The decrease in the yields of the reaction after each use of IL could possibly be due to the fact that we could not manage to recover the catalyst quantitatively after each run. Consequently, we repeated the reaction with lower amounts of catalyst. To test this idea, we repeated the reaction by adding some fresh catalyst to the IL recovered after the first use and the result was the same as the first run (Table 2, No. 1). Moreover, we observed a slight change in appearance for the recovered IL,

Table 1

Prolinium nitrate ([Pro]NO_3) promoted preparation of 2-(4-chlorophenyl)benzimidazole (**3e**) under various conditions.

Entry	Amount of IL (mol %)	Temperature (°C)	Time (min)	Product (%)[a] 3	4
1	20	r.t.	20	89	–
2	20	60	20	89	Trace
4	40	r.t.	25	89	–
5	40	60	25	89	Trace
7	60	r.t.	25	85	Trace
8	60	60	25	70	20
10	100	r.t.	50	85	15
11	100	100	40	80	20

[a] Isolated yield.

Table 2

Results for reusability of IL [Pro]NO_3 in the process of 2-(4-chlorophenyl)benzimidazole (3e) synthesis.

Run no.	Recovery percent	Reaction time (min)	Yield (%)[a]
1	95	30	89
2	90	40	82
3	90	55	78
4	90	60	70

[a] Isolated yield.

which would be due to trace impurities from the reaction. These changes in appearance were observed more obviously after any recovery.

To evaluate the scope and limitations of this IL under solvent-free condition various benzaldehyde derivatives and different derivatives of *o*-phenylenediamines were examined (Table 3, entries 1–17). Among the various benzaldehydes tested, the best yields were achieved for benzaldehydes with electron-withdrawing substituents (Table 3, entries 4–7). While among *o*-phenylenediamine derivatives the yield of products obtained from 4-nitro-*o*-phenylenediamine were high and the rates of reactions were also remarkable (Table 3, entries 8–12). In all reactions, byproduct **4** was not observed by TLC. Only in the case of 4-methylbenzaldehyde as reactant (Table 3, entry 11), the reaction rate was relatively long and the yield was moderate not high. Repeating the reaction with 3,4-diaminobenzoic acid showed the best yield and reactivity for 4-nitrobenzaldehyde (Table 3, entry 17) and the other derivatives were also synthesized with interesting yield. These results demonstrate a great level of versatility and efficiency for the synthesis of 2-arylbenzimidazole derivatives.

To complete evaluation of chemoselectivity, our attempts were focused on performing the reaction with a new variation. At this stage, we carried out the model reaction of *o*-phenylenediamine derivatives (1 mmol) with 4-chlorobenzaldehyde (2 mmol) under optimal conditions (r.t. and 20% of IL relative to *o*-phenylenediamine derivatives). Surprisingly, even after 3 h, no byproduct **4** (**4e**, **4i**, and/or **4n**) were formed and TLC analysis showed only the presence of products **3** (**3e**, **3i**, and/or **3n**) with the excess amount of benzaldehydes used.

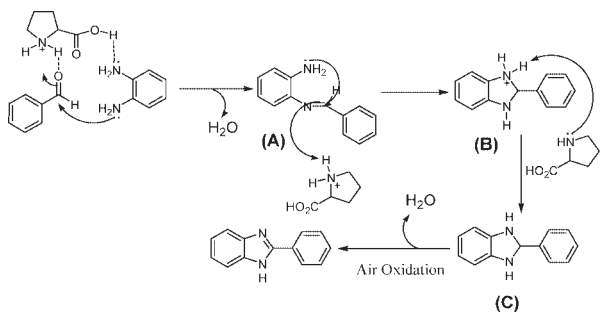
Table 3

Synthesis of 2-phenylbenzimidazole derivatives using amino acid based IL [pro]NO_3.

Entry	R_1	R_2	Time (min)	Product	Yield (%)[a]
1	H	H	50	3a	85
2	H	Me	45	3b	82
3	H	Ome	45	3c	85
4	H	Br	30	3d	93
5	H	Cl	30	3e	89
6	H	F	20	3f	81
7	H	NO_2	25	3g	90
8	NO_2	Br	60	3h	92
9	NO_2	Cl	50	3i	93
10	NO_2	CN	45	3j	95
11	NO_2	Me	80	3k	76
12	NO_2	NO_2	25	3l	85
13	CO_2H	Br	45	3m	86
14	CO_2H	Cl	45	3n	90
15	CO_2H	CN	30	3o	88
16	CO_2H	Me	60	3p	80
17	CO_2H	NO_2	20	3q	92

[a] Isolated yield.

Scheme 2



According to these findings, a proposed reaction pathway for the synthesis of 2-arylbenzimidazoles is shown in Scheme 2. As can be seen, prolinium cation from IL first interacts with both reactants to form the Schiff base intermediate (A) which then undergoes cyclization *via* intramolecular attack by another amino moiety on Schiff base to form protonated benzimidazoline intermediate (B). Then, this intermediate would be deprotonated to 2,3-dihydrobenzimidazoline (C). Finally, the intermediate (C) would be aromatized by air oxidation under reaction vessel conditions.

In summary, we have developed an efficient, eco-friendly as well as solvent and oxidant-free protocol for the synthesis of 2-arylbenzimidazole derivatives starting from phenylenediamine derivatives and diverse benzaldehydes using fully ''green'' IL L-prolinium nitrate as catalyst. The yields of products are very good to excellent and use of toxic solvents is avoided. Synthesis of some novel 2-arylbenzimidazole derivatives under mild conditions is the most important aspect of this study. Simple work-up and high degree of IL reusability are other interesting points of the developed procedure.

EXPERIMENTAL

Melting points were recorded on a Buchi B-540 apparatus. IR spectra were recorded on an ABB Bomem Model FTLA200-100 instrument. ^1H and ^{13}C NMR spectra were measured with a Bruker DRX-300 Avance spectrometer at 300 and 75 MHz using TMS as an internal standard. Chemical shifts (δ) are reported relative to TMS, and coupling constants (J) are reported in Hertz (Hz). Mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer with 70 eV ionization potential. Elemental analyses of new compounds were performed with a Vario EL III 0 Serial No. 11024054 instrument.

Typical experimental procedure for the preparation of substituted 2-arylbenzimidazoles using [Pro]NO_3 as catalyst. To a mixture of 4-chlorobenzaldehyde (3 mmol) and *o*-phenylenediamine (3 mmol) was added prolinium nitrate (prepared according to literature [22]) (0.6 mmol, 20% relative to reactants). The reaction mixture was stirred at 30°C and monitored by TLC (ethyl acetate:petroleum ether, 1:4). After completion of the reaction, water (10 mL) was added and the mixture was scratched and stirred for at least 30 min. The aqueous layer was filtered and the residues were purified by crystallization from EtOH:Water mixture. The product **3e** was obtained with 89% yield.

Aqueous layer containing IL was concentrated *in vacuo* to recycle and reuse the prolinium nitrate in another reaction.

Spectral and analytical data for substituted 2-arylbenzimidazoles.

2-Phenylbenzimidazole (3a). Light yellow solid; mp 283–285°C (Lit. [19] mp 289–291°C). IR (KBr): 1621 (C=N), 3447 cm^{-1} (NH). ^1H NMR (300 MHz, DMSO-d_6): δ 13.31 (s, 1H), 8.27 (d, 2H, J = 3.0), 7.69 (m, 2H), 7.59 (s, 3H), 7.34 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 114.65, 123.62, 127.13, 127.35, 129.20, 131.23, 136.34, 150.16.

2-(4-Methylphenyl)benzimidazole (3b). Light yellow solid; mp 268–270°C (Lit. [24] mp 277°C). IR (KBr): 1617 (C=N), 3060, 3435 (NH) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 12.87 (s, 1H), 8.10 (d, 2H, J = 8.1 Hz), 7.61 (m, 2H), 7.33 (d, 2H, J = 8.1 Hz), 7.19 (m, 2H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.96, 111.21, 118.72, 121.59, 126.42, 127.50, 129.52, 139.56, 151.45.

2-(4-Methoxyphenyl)benzimidazole (3c). Light yellow solid; mp 217–220°C (Lit. [19] mp 224–226°C). IR (KBr): 1612 (C=N), 3420 cm^{-1} (NH). ^1H NMR (300 MHz, DMSO-d_6): δ 12.73 (s, 1H), 8.11 (d, 2H, J = 9.0 Hz), 7.54 (s, 2H), 7.16 (m, 2H), 7.11 (d, 2H, J = 9.0 Hz), 3.82 (s, 3H).

2-(4-Bromophenyl)benzimidazole (3d). Light yellow solid; mp 294–296°C (Lit. [19] mp 299–300°C). IR (KBr): 1597 (C=N), 3420 cm^{-1} (NH). ^1H NMR (300 MHz, DMSO-d_6): δ 12.99 (s, 1H), 8.12 (d, 2H, J = 9.0 Hz), 7.75 (d, 2H, J = 9.0 Hz), 7.65 (m, 1H), 7.53 (m, 1H), 7.21 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 111.43, 118.98, 121.86, 123.26, 128.35, 129.39, 131.98, 150.22.

2-(4-Chlorophenyl)benzimidazole (3e). Light yellow solid; mp 283–286°C (Lit. [19] mp 292–294°C). IR (KBr): 1597 (C=N), 3420 cm^{-1} (NH). ^1H NMR (300 MHz, DMSO-d_6): δ 12.98 (s, 1H), 8.18 (d, 2H, J = 9.0 Hz), 7.62 (d, 3H, J = 9.0 Hz), 7.52 (d, 1H, J = 6.0 Hz), 7.21 (m, 2H).

2-(4-Fluorophenyl)benzimidazole (3f). Light yellow solid; mp 242–245°C (Lit. [19] mp 250–251°C). IR (KBr): 1602 (C=N), 3405 cm^{-1} (NH). ^1H NMR (300 MHz, DMSO-d_6): δ 12.92 (s, 1H), 8.22 (m, 2H), 7.58 (m, 2H), 7.39 (t, 2H, J = 6.0 Hz), 7.19 (d, 2H, J = 6.0 Hz).

2-(4-Nitrophenyl)benzimidazole (3g). Light red solid; mp 307–309°C (Lit. [19] mp 316°C). IR (KBr): 1606 (C=N), 3409 cm^{-1} (NH). ^1H NMR (300 MHz, DMSO-d_6): δ 13.28 (s, 1H), 8.40 (m, 4H), 7.65 (m, 2H), 7.26 (m, 2H).

2-(4-Bromophenyl)-5-nitrobenzimidazole (Mixture of tautomeric 3h and 4h). Yellow solid; mp 161–164°C. IR (KBr): 1608 (C=N), 3481 cm^{-1} (NH). ^1H NMR (300 MHz, DMSO-d_6): δ 13.64 (s, 1H), 8.11 (d, 1H, J = 8.4 Hz), 8.01 (d, 3H, J = 9 Hz), 7.91 (dd, 1H, J_1 = 9.0 Hz, J_2 = 2.4 Hz), 7.78 (d, 1H, J = 8.4 Hz), 7.70 (d, 3H, J = 9 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 108.05, 112.88, 113.13, 115.60, 124.55, 125.20, 128.24, 128.87, 131.00, 131.71, 132.20, 133.47, 133.96, 135.26, 135.90, 142.81, 143.36, 151.18, 158.54. MS (EI): m/e = 318 (M^+), 272, 162, 116. *Anal*. Calcd. For $C_{13}H_8BrN_3O_2$: C, 49.06; H, 2.52; N, 13.21. Found: C, 48.89; H, 3.0; N, 13.23.

2-(4-Chlorophenyl)-5-nitrobenzimidazole (3i). Yellow solid; mp 277–281°C. IR (KBr): 1601 (C=N), 3281 cm^{-1}(NH). ^1H NMR (300 MHz, DMSO-d_6): δ 13.60 (s, 1H), 8.41 (s, 1H), 8.16 (d, 2H, J = 7.5 Hz), 8.08 (d, 1H, J = 8.4 Hz), 7.71 (d, 1H, J = 8.4 Hz), 7.62 (d, 2H, J = 7.5 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 118.08, 120.60, 122.3, 123.64, 127.85, 128.63, 129.23, 135.66, 136.59, 142.75, 154.62. Ms (EI): m/e = 273 (M^+), 227, 192, 111. *Anal*. Calcd. for $C_{13}H_8ClN_3O_2$: C, 57.05; H, 2.95; N, 15.35. Found: C, 57.44; H, 2.61; N, 15.62.

2-(4-Cyanophenyl)-5-nitrobenzimidazole (Mixture of tautomeric 3j and 4j). Yellow solid; mp 190–193°C. IR (KBr): 1602 (C=N), 2228 (C≡N), 3363 cm^{-1} (NH). ^1H NMR (300 MHz, DMSO-d_6): δ 13.73 (s, 1H), 8.88 (s, 1H), 8.41–7.73 (m, 12H), 6.88 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 112.88, 113.20, 118.39, 118.66, 124.93, 127.46, 129.60, 132.52, 132.73, 133.00, 135.85, 139.96, 142.98, 151.43, 153.73, 157.75. MS (EI): m/e = 264 (M^+), 218, 192, 162, 118. *Anal*. Calcd. for $C_{14}H_8N_4O_2$: C, 63.64; H, 3.05; N, 21.20. Found: C, 63.98; H, 2.77; N, 20.88.

2-(4-Methylphenyl)-5-nitrobenzimidazole (3k). Yellow solid; mp 211–214°C. IR (KBr): 1637 (C=N), 3435 cm^{-1}(NH). ^1H NMR (300 MHz, DMSO-d_6): δ 13.53 (s, 1H), 7.39 (d, 2H, J = 9.0 Hz), 6.54 (d, 1H, J = 12.0 Hz), 6.04 (s, 2H), 5.06 (s, 2H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.08, 108.03, 111.44, 115.61, 126.98, 129.78, 133.96, 136.79, 143.36, 153.14. MS (EI): m/e = 253 (M^+), 153, 107, 80. *Anal*. Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.39; H, 4.38; N, 16.59. Found: C, 66.28; H, 4.09; N, 16.34.

2-(4-Nitrophenyl)-5-nitrophenylbenzimidazole (Mixture of tautomeric 3l and 4l). Red solid; mp 222–224°C. IR (KBr): 1612 (C=N), 3101, 3388, 3486 (NH) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 8.98 (s, 2H), 8.32 (s, 4H), 8.11 (s, 1H), 7.94 (d, 1H, J = 9 Hz), 6.91 (s, 2H), 6.78 (d, 1H, J = 9 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 113.26, 113.39, 122.27, 123.63, 123.77, 125.09, 130.11, 132.72, 135.88, 136.49, 141.69, 148.77, 151.51, 157.41. MS (EI): m/e = 284 (M^+), 238, 192, 164, 118. *Anal*. Calcd for $C_{13}H_8N_4O_4$: C, 51.41; H, 3.77; N 18.59. Found: C, 51.88; H, 4.13; N, 18.20.

2-(4-Bromophenyl)benzimidazole-5-carboxylic acid (3m). Pale yellow solid; mp 183–185°C. IR (KBr): 1635 (C=N), 1678 (C=O), 3091, 3379 (NH) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 13.49 (s, 1H), 12.74 (s, 1H), 8.14 (m, 3H), 7.80 (m, 3H), 7.65 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 123.88, 124.79, 128.64, 128.82, 132.09, 151.95, 167.76. MS (EI): m/e = 316 (M^+ − 1), 273, 271, 191. *Anal*. Calcd. for $C_{14}H_9BrN_2O_2$: C. 53.02; H, 2.86; N, 8.83. Found: C. 53.11; H, 2.54; N, 8.75.

2-(4-Chlorophenyl)benzimidazole-5-carboxylic acid (3n). Pale yellow solid; mp 168–169°C. IR (KBr): 1622 (C=N), 1683 (C=O), 3101, 3414 (NH) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 13.29 (s, 1H), 12.76 (s, 1H), 8.20 (d, J = 9 Hz, 3H), 7.84 (m, 1H), 7.64 (d, J = 9 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 123.67, 124.55, 128.45, 128.51, 129.20, 135.10, 147.1, 154.32, 156.63, 167.80. MS (EI): m/e = 272 (M^+), 227, 192. *Anal*. Calcd. for $C_{14}H_8ClN_2O_2$: C, 61.89; H, 2.97; N, 10.31. Found: C, 62.14; H, 2.69; N, 10.12.

2-(4-Cyanophenyl)benzimidazole-5-carboxylic acid (Mixture of tautomeric 3o and 4o). Pale yellow solid; mp 183–185°C. IR (KBr): 1606 (C=N), 2228 (C≡N), 3368 cm^{-1} (NH). ^1H NMR (300 MHz, DMSO-d_6): δ 13.48 (s, 1H), 13.05 (s, 1H), 8.14 (m, 3H), 7.82 (m, 3H), 7.67 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 112.43, 112.80, 113.72, 117.28, 118.54, 118.76, 125.23, 127.32, 129.33, 130.21, 132.57, 133.06 (2 × C), 133.72, 140.44, 148.96, 151.68, 155.43, 167.51, 167.71. MS (EI): *m/e* = 263 (M^+), 246, 218, 116. *Anal*. Calcd. for $C_{15}H_9N_3O_2$: C, 64.76; H, 3.64; N, 15.11. Found: C, 64.27; H, 3.94; N, 14.66.

2-(4-Methylphenyl)benzimidazole-5-carboxylic acid (mixture of tautomeric 3p and 4p). Pale yellow solid; mp 200–205°C. IR (KBr): 1628 (C=N), 1689 (C=O), 3369 (NH), 3426 (OH) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 12.70 (s, 1H), 8.16 (s, 1H), 8.08 (d, 2H, *J* = 6.0 Hz), 7.82 (d, 1H, *J* = 6.0 Hz), 7.63 (d, 1H, *J* = 6.0 Hz), 7.36 (d, 2H, *J* = 6.0 Hz), 2.49 (s, 2H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.56, 21.01, 123.47, 124.46, 126.69, 126.86, 129.82, 140.27, 153.70, 167.87. MS (EI): *m/e* = 252 (M^+), 237, 207. *Anal*. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.35; H, 4.61; N, 10.98.

2-(4-Nitrophenyl)benzimidazole-5-carboxylic acid (mixture of tautomeric 3q and 4q). Pale red solid; mp 270–272°C. IR (KBr): 1602 (C=N), 1671(C=O), 3394 (NH), 3501(OH) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 13.62 (s, 1H), 12.50 (s, 1H), 8.92 (s, 1H), 8.44 (m, 3H), 8.32 (s, 4H), 8.24 (s, 0.5H), 8.14 (m, 0.8H), 7.88 (m, 0.5H), 7.72 (s, 0.7H), 7.61 (d, 1H, *J* = 6.0 Hz), 6.75 (d, 1H, *J* = 6.0 Hz).^{13}C NMR (75 MHz, DMSO-d_6): δ 113.80, 117.32, 118.54, 123.80 (2 × C), 124.37, 127.82, 129.75, 130.36, 130.66, 133.01, 142.18, 148.18, 148.54, 149.05, 154.96, 167.49, 167.69. MS (EI): *m/e* = 283 (M^+), 238, 192. *Anal*. Calcd. for $C_{14}H_9N_3O_4$: C, 56.43; H, 3.28; N, 13.79. Found: C, 56.07; H, 3.67; N, 13.41.

Acknowledgments. The authors gratefully acknowledge Research Council of K. N. Toosi University of Technology for partial financial support and Dr. Khosrow Jadidi from Shahid Beheshti University for helpful consultations.

REFERENCES AND NOTES

[1] (a) Tamm, I. Science 1954, 126, 1235; (b) Migawa, M. T.; Giradet, J. L.; Walker, J. A.; Koszalka, G. W.; Chamberlain, S. D.; Drach, J. C.; Townsend, L. B. J Med Chem 1998, 41, 1242; (c) Porcari, A. R.; Devivar R. V.; Kucera, L. S.; Drach, J. C.; Townsend, L. B. J Med Chem 1998, 41, 1252.

[2] Kim, J. S.; Gatto, B.; Yu, C.; Liu, A.; Liu, L. F.; LaVioe, E. J Med Chem 1996, 39, 992.

[3] Zarrinmayeh, H.; Zimmerman, D. M.; Cantrell, B. E.; Schober, D. A.; Bruns, R. F Bioorg Med Chem Lett 1999, 9, 647.

[4] Denny, W. A.; Rewcastle, G. W.; Bagley, B. C J Med Chem 1990, 33, 814.

[5] Forseca, T.; Gigante B.; Gilchrist T. L. Tetrahedron 2001, 57, 1793.

[6] Zhao, J.; Arnaiz, D.; Griedel, B.; Sakata, B.; Dallas, J.; Whitlow, M.; Trinh, L.; Post, J.; Liang, A.; Morrissey, M.; Shaw, K. Bioorg Med Chem Lett 2000, 10, 963.

[7] (a) Grimmet, M. R. In Comprehensive Heterocyclic Chemistry; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 5, pp 457–480; (b) Harapanhalli, R. S.; McLaughlin, L. W.; Howell, R. W.; Rao, D. V.; Adelstein, S. J.; Kassis, A. I. J Med Chem 1996, 39, 4804.

[8] Verner, E.; Katz, B. A.; Spencer, J. R.; Allen, D.; Hataye, J.; Hruzewicz, W.; Hui, H. C.; Kolesnikov, A.; Li, Y.; Luong, C.; Martelli, A.; Radika, K.; Rai, R.; She, M.; Shrader, W.; Sprengeler, P. A.; Trapp, S.; Wang, J.; Young, W. B.; Mackman, R. L. J Med Chem 2001, 44, 2753.

[9] Vanden Eynde, J. J.; Delfosse, F.; Lor, P.; Van Haverbeke, Y. Tetrahedron 1995, 51, 5813.

[10] Chikashita, H.; Nishida, S.; Miyazaki, M.; Morita, Y.; Itoh, K. Bull Chem Soc Jpn 1987, 60, 737.

[11] Patzold, F.; Zeuner, F.; Heyer, T. H.; Niclas, H. J. Synth Commun 1992, 22, 281.

[12] Bhatnagar, I.; George, M. V. Tetrahedron 1968, 24, 1293.

[13] Stephens, F. F.; Bower, J. D. J Chem Soc 1949, 2971.

[14] Beaulieu, P. L.; Haché, B.; von Moos, E. A. Synthesis 2003, 1683.

[15] Weidner-Wells, M. A.; Ohemeng, K. A.; Nguyen, V. N.; Fraga-Spano, S.; Macielag, M. J.; Werblood, H. M.; Foleno, B. D.; Webb, G. C.; Barrett, J. F.; Hlasta, D. J. Bioorg Med Chem Lett 2001, 11, 1545.

[16] Lin, S.; Yang, L. Tetrahedron Lett 2005, 46, 4315.

[17] Gogoi, P.; Konwar, D. Tetrahedron Lett 2006, 47, 79.

[18] Du, L-.H.; Wang, Y.-G. Synthesis 2007, 675.

[19] Varala, R.; Nasreen, A.; Enugala, R.; Adapa, S. R. Tetrahedron Lett 2007, 48, 69.

[20] (a) Anastas, P. T.; Kirchhoff, M. M. Acc Chem Res 2002, 35, 686; (b) Cole, A. C.; Jensen, J. L.; Ntai, I.; Tran, K. L. T.; Weaver, K. J.; Forbes, D. C.; Davis, J. H., Jr. J Am Chem Soc 2002, 124, 5962.

[21] Ma, H. Q.; Wang, Y. L.; Li, J. P.; Wang, J. Y. Heterocycles 2007, 71, 135.

[22] Tao, G.-H.; He, L.; Liu, W.; Xu, L.; Xiong, W.; Wang, T.; Kou, Y. Green Chem 2005, 8, 639.

[23] Alloum, A. B.; Bougrin, K.; Soufiaoui, M. Tetrahedron Lett 2003, 44, 5935.