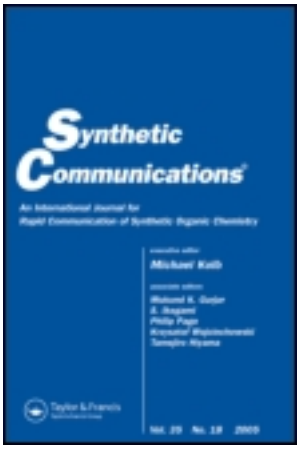



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# Efficient and Inexpensive Synthesis of Benzimidazoles and Quinoxalines

B. China Raju [a], N. Dharma Theja [a] & J. Ashok Kumar [a]

[a] Natural Products Laboratory, Organic Chemistry Division 1, Indian Institute of Chemical Technology, Hyderabad, India

Version of record first published: 15 Feb 2011

To cite this article: B. China Raju, N. Dharma Theja & J. Ashok Kumar (2008): Efficient and Inexpensive Synthesis of Benzimidazoles and Quinoxalines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:1, 175-188

To link to this article: http://dx.doi.org/10.1080/00397910802372525

*Synthetic Communications*®, 39: 175–188, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802372525

Taylor & Francis
Taylor & Francis Group



# Efficient and Inexpensive Synthesis of Benzimidazoles and Quinoxalines

**B. China Raju, N. Dharma Theja, and J. Ashok Kumar**
Natural Products Laboratory, Organic Chemistry Division 1, Indian Institute of Chemical Technology, Hyderabad, India

**Abstract:** *o*-Phenylenediamines were reacted with carbonyl compounds, β-ketoesters, and 1,2-diketones in presence of ammonium salts to give benzimidazoles and quinoxalines in very good yields. Ammonium salts are commercial and environmentally benign catalysts.

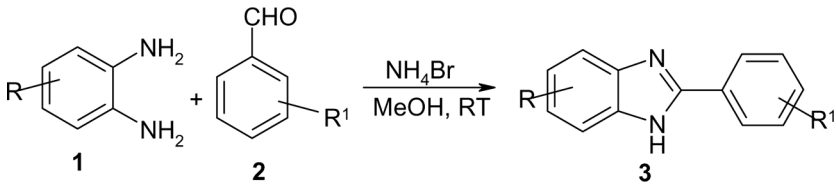
**Keywords:** Ammonium salts, benzimidazoles, 1,2-diketones, β-ketoesters, OPDA, quinoxalines

Benzimidazoles and its derivatives are well documented in the literature to exhibit a wide range of biological activities. They are potent inhibitors of TIE-2 and VEGFR-2 tyrosine kinase receptors,[1] antitumor agents,[2] gamma-aminobutyric acid (GABA) agonists,[3] and 5-HT3 antagonists.[4] Similarly, quinoxaline- containing antibiotics such as actinomycin, levomycin, and echinomycin are known to inhibit the growth of gram-positive bacteria and are active against various transplantable tumors.[5] The general synthesis of benzimidazoles is by the condensation reaction of 1,2-phenylenediamine with carboxaldehydes, carboxylic acids,[6] or their derivatives[7] such as chlorides, nitriles, and orthoesters under strong acidic conditions with high temperatures. The most common method for quinoxalines is aryl 1,2-diamines with 1,2-dicarbonyl compounds in refluxing ethanol in the presence of acetic acid.[8] Other methods developed include

Received April 10, 2008.
Address correspondence to B. China Raju, Natural Products Laboratory, Organic Chemistry Division 1, Indian Institute of Chemical Technology, Hyderabad 500 607, India. E-mail: chinarajuiict@yahoo.co.in

metal precursors, acids, zeolites,[9] microwave,[10] and solid-phase synthesis.[11] Recently $I_2$[12] and $NH_2SO_3H$[13] were also reported in the literature.

Ammonium halides[14] are inexpensive, commercially available reagents for few organic transformation reactions such as halogenation of aromatic compounds and synthesis of 3,4-dihydropyrimidine-2(1*H*)-ones. However, there are no reports of the use of ammonium salts as catalyst for the synthesis of benzimidazoles and quinoxalines. In continuation of our efforts on synthesis of heterocycles[15] and on development of synthetic methodologies,[16] herein we report a facile method for the synthesis of benzimidazoles and quinoxalines by the condensation of 1,2-phenylenediamine with carbonyl compounds, β-ketoesters, and 1,2-diketones in the presence of ammonium salts in very good yields. It is known that the reaction of O-phenylenediamine (OPDA) with carbonyl compounds under strong acidic conditions gives benzimidazoles, whereas OPDA in the presence of β-ketoesters under neutral reflux conditions gives benzodiazepin-2-ones, with the elimination of water and alcohol. Under acidic conditions, initially it forms ethyl β-2-amino aniline crotonate at room temperature; upon heating it gives 2-methyl-1*H*-benzo[*d*]imidazole instead of benzodiazepin-2-ones with the elimination of ethyl acetate. So we made an attempt to react OPDA with carbonyl compounds and β-ketoesters with different ammonium salts to see the feasibility of the formation of compounds. To select favorable reaction conditions, we first examined the model reaction of 1,2-phenylenediamine (1 mol) with benzaldehyde (1 mol) in the presence of $NH_4Cl$ (1 mol) under solvent-free conditions at room temperature. The reaction was monitored by thin-layer chromatography (TLC) and 2-phenyl-1*H*-benzo[*d*]imidazole obtained in 10% yield. Similarly the reaction was conducted in different solvents such as $CH_3CN$, MeOH, $CHCl_3$, ether, and DMF; methanol is found to be the most suitable solvent to give benzimidazole in 30% yield. Next we carried out the same reaction with different ammonium salts such as $NH_4F$, $NH_4Br$, $NH_4NO_3$, $(NH_4)_2CO_3$, and $(NH_4)_2SO_4$ in the presence of methanol at room temperature; among these $NH_4Br$ (4 mol) gave 2-phenyl-1*H*-benzo[*d*]imidazole in 94% yield 4 h (Scheme 1, Table 1, entry 2). The results, tabulated in Table 2, indicate the formation of benzimidazoles.




***Scheme 1.*** Ammonium halide catalyzed synthesis of 2-arylbenzimidazoles.

**Table 1.** Optimization of reaction conditions for the synthesis of 2-phenyl benzimidazole by the condensation of OPDA with benzaldehyde using various ammonium salts at room temperature in MeOH

| Entry | $NH_4X$[a] | Time (h) | Yield (%)[b] |
|---|---|---|---|
| 1 | $NH_4Cl$ | 4 | 90 |
| 2 | $NH_4Br$ | 4 | 94 |
| 3 | $NH_4F$ | 5 | 78 |
| 4 | $NH_4NO_3$ | 6 | 80 |
| 5 | $(NH_4)_2SO_4$ | 10 | 84 |
| 6 | $(NH_4)_2CO_3$ | 12 | 52 |

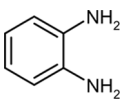
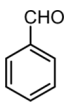
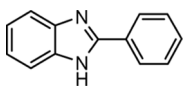
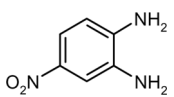
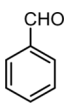
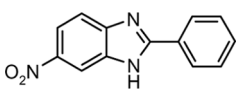
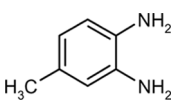
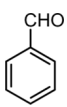
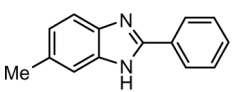
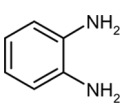
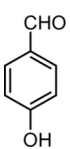
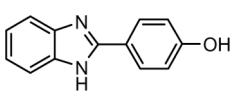
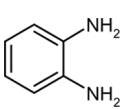
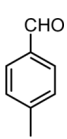
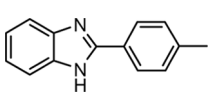
[a]Reaction carried out with 4 mol of $NH_4X$.
[b]Isolated and unoptimized yields.

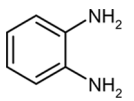
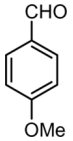
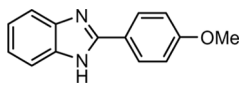
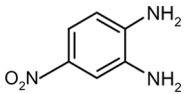
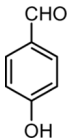
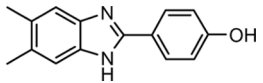
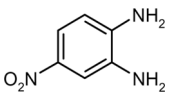
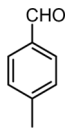
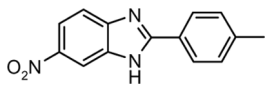
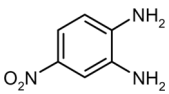
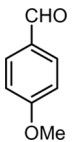
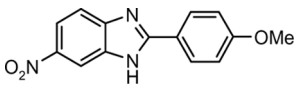


Next we studied the reaction of OPDA (1 mol) with ethyl acetoacetate **4a** (1 mol) in the presence of $NH_4Cl$ (1 mol) at room temperature: the reaction is futile. Similarly the reaction was carried out at 85 °C under solvent-free conditions (20 min, TLC) to afford 2-methyl-1*H*-benzo[*d*]imidazole **5a** in 96% yield (Scheme 2). The obtained product was confirmed based on spectral data ($^1$H NMR and MS). Then we carried out the reaction with different ammonium salts such as $NH_4F$, $NH_4Br$, $NH_4NO_3$, $(NH_4)_2CO_3$, $(NH_4)_2SO_4$, $NH_4OAc$, and $(NH_4)_2S_2O_8$; among these $NH_4Br$ gives the better yield (Table 3, entry 2, 98%). The results, tabulated in Table 4, indicate the formation of 2-methylbenzimidazoles in very good yields. The results encouraged us to carry out the reactions with substituted OPDA and β-ketoesters; the obtained results, tabulated in Table 3, indicate the formation of substituted benzimidazoles (Table 4, entry 5a–i). All the products were well characterized based on spectral data ($^1$H NMR, IR, and MS).

Similarly, next we carried out the reaction of OPDA **1a** (1 mol), benzil **6a** (1 mol), and $NH_4Br$ (1 mol) in the presence of $CH_3CN$ at room temperature (5 min, TLC), which gave 2,3-diphenylquinoxaline **7a** in 98% yield (Scheme 3). The product was well characterized by its spectral data ($^1$H NMR, IR, and MS). The results encouraged us to carry out the reaction with different substituted OPDA with 1,2-diketones in the presence of $NH_4Br$ at room temperature, but the reactions were sluggish at room temperature, whereas under reflux conditions quinoxalines **7a**–**f** were obtained in very good yields with $NH_4Br$ (4 mol). The results were tabulated in Table 5, and all the products were well characterized based on spectral data ($^1$H NMR, IR, and MS). Under similar conditions, the attempted reaction of OPDA with 1,3-diketones such as dibenzoyl methane gave 2-phenylbenzimidazole instead of benzodiazepine. The reactions of OPDA with 1,3-diketones are presently under investigation.

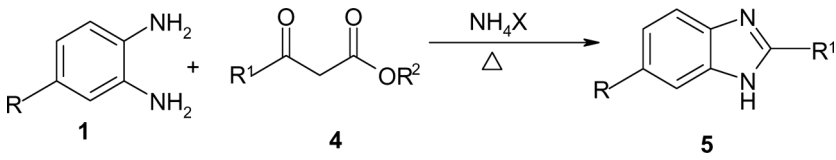
**Table 2.** Synthesis of benzimidazoles

| Entry | OPDA (**1**) | Aldehyde (**2**) | Time (h) | Product (**3**) | Yield (%)[a] | MP (°C, lit.)[Ref.] |
|---|---|---|---|---|---|---|
| a |  |  | 4 |  | 94 | 294–296 (295–297)[17] |
| b |  |  | 18 |  | 82 | 206–209 (207–208)[18] |
| c |  |  | 6 |  | 80 | 244–246 (242–244)[18] |
| d |  |  | 16 |  | 72 | 272–274 (271)[17] |
| e |  |  | 6 |  | 82 | 278–282 (277–278)[19] |

| | | | | | | |
|---|---|---|---|---|---|---|
| f |  |  | 6 |  | 75 | 230–232 (284–288)[19] |
| g |  |  | 6 |  | 78 | 283–286 |
| h |  |  | 8 |  | 65 | 221–224 |
| i |  |  | 8 |  | 65 | 234–236 (237–238)[20] |

[a]Isolated and unoptimized yields.

*Note*. All the compounds (**3a–i**) were characterized by their spectral data ($^1$H NMR, IR, and MS) and compared with authentic samples.




***Scheme 2.*** Synthesis of substituted benzimidazoles.

In conclusion we devised an efficient, inexpensive protocol for the synthesis of benzimidazoles and quinoxalines using readily available and inexpensive reagents under mild conditions with very good yields.

## EXPERIMENTAL

$^1$H NMR spectra were recorded on a Varian Gemini 200- and 300-MHz instrument in $CDCl_3$, DMSO-$d_6$ using TMS as an internal standard. The mass spectra were measured on a LCMS Agilent mass spectrometer. The IR spectra were recorded on a Nicolet 740 FT IR spectrometer. Melting points were measured in a Buchi-510 apparatus and are uncorrected.

### General Procedure

Typical Experimental Procedure for the Synthesis of Benzimidazoles

Benzaldehyde (**2a,** 1 mmol) was added to a stirred solution of 1,2-phenylenediamine (**1,** 1 mmol) and $NH_4Br$ (4 mmol) in methanol (5 ml) for 5 min at room temperature. Stirring was continued for 4 h. After completion of the reaction (TLC), the solvent was removed under reduced pressure and

**Table 3.** Optimization of reaction conditions for the synthesis of 2-methyl benzimidazole by the condensation of OPDA with EAA using various ammonium salts at 85 °C

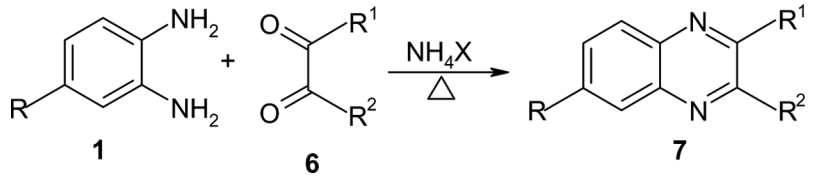
| Entry | $NH_4X$ | Time (min) | Yield (%)[a] |
|---|---|---|---|
| 1 | $NH_4Cl$ | 25 | 96 |
| 2 | $NH_4Br$ | 20 | 98 |
| 3 | $NH_4F$ | 25 | 88 |
| 4 | $NH_4NO_3$ | 35 | 82 |
| 5 | $(NH_4)_2SO_4$ | 40 | 92 |
| 6 | $(NH_4)_2CO_3$ | 40 | 56 |
| 7 | $NH_4OAc$ | 40 | 65 |
| 8 | $(NH_4)_2S_2O_8$ | 60 | 62 |

[a]Isolated and unoptimized yields.

**Table 4.** Synthesis of substituted benzimidazoles using $NH_4Br$

| Entry | Aryl diamine (**1**) | β-ketoester (**4**) | Time (min) | Temp (°C) | Product (**5**) | Mp (°C, lit.)[Ref.] | Yield (%)[a] |
|---|---|---|---|---|---|---|---|
| a | OPDA | Ethyl acetoacetate | 25 | 85 | 2-Methyl benzimidazole | 176–178 (182)[21] | 98 |
| b | OPDA | Methyl acetoacetate | 25 | 85 | 2-Methyl benzimidazole | 183–184 (182)[21] | 86 |
| c | OPDA | Phenyl acetoacetate | 45 | 85 | 2-Aryl benzimidazole | 296–299 (298–301)[17] | 82 |
| d | OPDA | Trifluoro ethyl acetoacetate | 60 | 100 | No reaction | — | — |
| e | Nitro OPDA | Ethyl acetoacetate | 60 | 85 | 2-Methyl-6-nitro-benzimidazole | 218–220 (222–224)[18] | 82 |
| f | Nitro OPDA | Methyl acetoacetate | 40 | 85 | 2-Methyl-6-nitro benzimidazole | 218–220 (222–224)[18] | 78 |
| g | Nitro OPDA | Trifluoro ethyl acetoacetate | 60 | 100 | No reaction | — | — |
| h | Methyl OPDA | Ethyl acetoacetate | 45 | 85 | 2,6-Dimethyl benzimidazole | 201–202 (202–204)[18] | 88 |
| i | Methyl OPDA | Methyl acetoacetate | 45 | 85 | 2,6-Dimethyl benzimidazole | 201–203 (202–204)[18] | 82 |

[a]All the reactions were carried out with 1 mol of $NH_4Br$; isolated yields and unoptimized yields.




***Scheme 3.*** Synthesis of quinoxalines.



extracted with ethyl acetate (2 × 20 ml); the organic layer was washed with water (2 × 10 ml). Layers were separated, and the organic layer was dried over sodium sulfate. Solvent was removed under reduced pressure, and crude product was subjected to column chromatography using petroleum ether/EtOAc (9:1), which gave 2-phenyl-1*H*-benzo[*d*]imidazole (**3a**) as a solid in 94% yield.

Typical Experimental Procedure for the Synthesis of Benzimidazoles

1,2-Phenylenediamine (**1, 1** mmol) and ethyl acetoacetate (**4a**, 1 mmol) in presence of $NH_4Br$ (1 mmol) were heated at 85 °C for 20 min. The reaction mixture was cooled, extracted with ethyl acetate (2 × 20 ml), and washed with water (2 × 10 ml). The layers were separated, the organic layer was dried over sodium sulfate, solvent was removed under reduced pressure, and crude product was subjected to column chromatography using petroleumether/EtOAc (9:1) to give 2-methyl-1*H*-benzo[*d*]imidazole (**5a**) as a solid in 96% yield.

Typical Experimental Procedure for the Synthesis of Quinoxalines

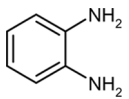
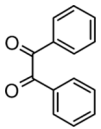
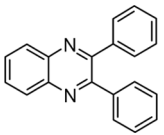
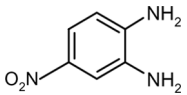
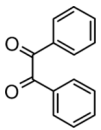
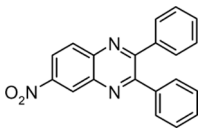
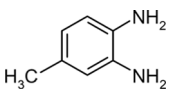
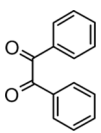
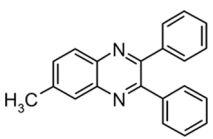
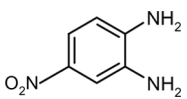
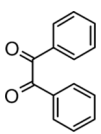
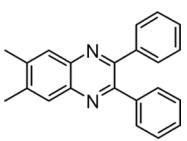
4-Nitro-1,2-phenylenediamine (**1**, 1 mmol), benzil (**6b**, 1 mmol), and $NH_4Br$ (4 mmol) were refluxed in acetonitrile for 45 min. The reaction mixture was cooled; solvent was removed under reduced pressure, extracted with ethyl acetate (2 × 20 ml), and washed with water (2 × 10 ml). The layers were separated, the organic layer was dried over sodium sulfate, and solvent was removed under reduced pressure to give 6-nitro-2,3-diphenylquinoxaline (**7b**) as a solid in 88% yield.

**Spectral Data**

4-(5,6-Dimethyl-1*H*-benzo[*d*]imidazol-2-yl) phenol (**3g**)

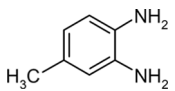
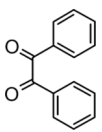
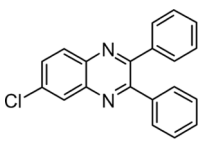
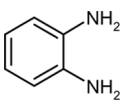
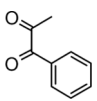
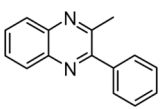
Solid; $^1$H NMR: δ 2.30 (s, 6H, $2CH_3$), 6.86 (d, 2H, aromatic), 7.28 (s, 2H, aromatic), 7.92 (d, 2H, aromatic; IR (KBr): 3426, 2923, 2855, 1742, 1631,

**Table 5.** Synthesis of quinoxalines using $NH_4Br$

| Entry | OPDA (**1**) | 1,2-Diketones (**6**) | Time (min) | Product (**7**) | Yield (%)[a] | Mp (°C, lit.)[Ref.] |
|---|---|---|---|---|---|---|
| a |  |  | 5 |  | 98 | 125–127 (126–127)[12] |
| b |  |  | 45 |  | 88 | 187–188 (187–187.9)[22] |
| c |  |  | 60 |  | 82 | 114–116 (118–118.5)[23] |
| d |  |  | 80 |  | 86 | 174–176 (173–175)[24] |

(*Continued*)

**Table 5.** Continued

| Entry | OPDA (**1**) | 1,2-Diketones (**6**) | Time (min) | Product (**7**) | Yield (%)[a] | Mp (°C, lit.)[Ref.] |
|---|---|---|---|---|---|---|
| e |  |  | 120 |  | 84 | 120–124 (122–123)[25] |
| f |  |  | 120 |  | 82 | 56–58 (53–55)[26] |

[a]Isolated and unoptimized yields.

1461, 1378, 1258, 1217, 1027, 760 $cm^{-1}$; mass (LCMS): $m/z$ 239 ($M^+ + H$). Anal. calcd. for $C_{15}H_{14}N_2O$: C, 75.63; H, 5.88; N, 11.76. Found: C, 75.59; H, 5.84; N, 11.79.

2-(4-Methylphenyl)-6-nitro-1*H*-benzo[*d*]imidazole (**3h**)

Solid; $^1H$ NMR: δ 2.44 (s, 3H, $CH_3$), 7.28 (d, 2H, aromatic), 7.60 (d, 1H, aromatic), 7.96 (d, 2H, aromatic), 8.16 (d, 1H, aromatic), 8.44 (s, 1H, aromatic); IR (neat): 2962, 2869, 1462, 1384, 1217, 760 $cm^{-1}$; mass (LCMS): $m/z$ 254 ($M^+ + H$). Anal. calcd. for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.34; N, 16.60. Found: C, 66.32; H, 4.37; N, 16.64.

2-Methyl-1*H*-benzo[*d*]imidazole (**5a**)

Solid; $^1H$ NMR: δ 2.64 (s, 3H, $CH_3$), 6.08 (bs, 1H, NH), 7.16–7.24 (m, 2H, aromatic), 7.50–7.58 (m, 2H, aromatic); IR (KBr): 3093, 3068, 2996, 1622, 1488, 1360, 896 $cm^{-1}$; mass (LCMS): $m/z$ 133 ($M^+ + H$).

2-Methyl-6-nitro-1*H*-benzo[*d*]imidazole (**5e**)

Solid, $^1H$ NMR: δ 2.64 (s, 3H, $CH_3$), 7.54 (d, 1H, aromatic), 8.12 (d, 1H, aromatic), 8.44 (s, 1H, aromatic); mass (LCMS): $m/z$ 178 ($M^+ + H$).

2,6-Dimethyl-1*H*-benzo[*d*]imidazole (**5h**)

Solid; $^1H$ NMR: δ 2.46 (s, 3H, $CH_3$), 2.64 (s, 3H, $CH_3$), 7.02 (d, 1H, aromatic), 7.32 (s, 1H, aromatic), 7.46 (s, 1H, aromatic), 9.48 (brs, 1H, NH); mass (LCMS): $m/z$ 147 ($M^+ + H$).

2,3-Diphenylquinoxaline (**7a**)

Solid; $^1H$ NMR: δ 7.24–7.38 (m, 6H, aromatic), 7.44–7.52 (m, 4H, aromatic), 7.72–7.80 (m, 2H, aromatic), 8.12–8.20 (m, 2H, aromatic); mass (LCMS): $m/z$ 283 ($M^+ + H$).

6-Nitro-2,3-diphenylquinoxaline (**7b**)

Solid, $^1H$ NMR: δ 7.30–7.44 (m, 6H, aromatic), 7.50–7.56 (m, 4H, aromatic), 8.26 (d, 1H, aromatic), 8.52 (d, 1H, aromatic), 9.06 (s, 1H, aromatic); mass (LCMS): $m/z$ 328 ($M^+ + H$).

2-Methyl-3-phenylquinoxaline (**7f**)

Solid, $^1$H NMR: δ 2. 78 (s, 3H, $CH_3$), 7.40–7.56 (m, 3H, aromatic), 7.58–7.76 (m, 4H, aromatic), 7.98–8.16 (m, 2H, aromatic); mass (LCMS): $m/z$ 221 ($M^+ + H$).

## ACKNOWLEDGMENTS

The authors are thankful to the head, Organic Chemistry Division 1, and the director, Indian Institute of Chemical Technology, for constant encouragement.



## REFERENCES

1. Hasegawa, M.; Nishigaki, N.; Washio, Y.; Kano, K.; Harris, P. A.; Sato, H.; Mori, I.; West, R. I.; Shibahara, M.; Toyoda, H.; Wang, L.; Nolte, R. T.; Veal, J. M.; Cheng, M. Discovery of novel benzimidazoles as potent inhibitors of TIE-2 and VEGFR-2 tyrosine kinase receptors. *J. Med. Chem.* **2007**, *50*, 4453.
2. Hranjec, M.; Kralj, M.; Piantanida, I.; Sedic, M.; Suman, L.; Pavelic, K.; Zamola, G. K. Novel cyano and amidino-substituted derivatives of styryl-2-benzimidazoles and benzimidazo[1,2-a]quinolines: Synthesis, photochemical synthesis, DNA, and antitumor evaluation, part 3. *J. Med. Chem.* **2007**, *50*, 5696.
3. Falco, J.; Pique, M.; Gonzalez, M.; Buira, I.; Mendez, E.; Terencio, J.; Perez, C.; Princep, M.; Palomer, A.; Guglietta, A. Synthesis, pharmacology, and molecular modeling of N-substituted 2-phenyl-indoles and benzimidazoles as potent $GABA_A$ agonists. *Eur. J. Med. Chem.* **2006**, *41*, 985.
4. Lopez, M. L. R.; Benhamu, B.; Morcillio, M. J.; Tejada, I. D.; Orensanz, L.; Alfaro, L.; Martin, M. I. Potential antitumor agents 59: Structure–activity relationships for 2-phenylbenzimidazole-4-carboxamides, a new class of minimal DNA-intercalating agents which may not act via topoisomerase II. *J. Med. Chem.* **1999**, *33*, 814.
5. Dell, A.; William, D. H.; Morris, H. R.; Smith, G. A.; Feeney, J.; Roberts, G. C. Structure revision of the antibiotic echinomycin. *J. Am. Chem. Soc.* **1975**, *97*, 2497.
6. (a) Phillips, M. A. The formation of 2-substituted benziminazoles. *J. Chem. Soc.* **1928**, 2393; (b) Grimmet, M. R.; Katritzky, A. R.; Rees, C. W. *Heterocyclic Chemistry*, Pergamon: Oxford, UK, 1984; vol. 5, p. 457.
7. (a) Czarny, A.; Wilson, W. D.; Boykin, D. W. Synthesis of mono-cationic and dicationic analogs of Hoechst 33258. *J. Heterocycl. Chem.* **1996**, *33*, 1393; (b) Tidwell, R. R.; Geratz, J. D.; Dann, O.; Volz, G.; Zeh, D.; Loewe. Diarylamidine derivatives with one or both of the aryl moieties consisting of an indole or indole like ring: Inhibitors of arginine specific esteroproteases. *J. Med. Chem.* **1978**, *21*, 613; (c) Fairley, T. A.; Tidwell, R. R.; Donkor, I.; Naiman, N. A.; Ohemengm,

K. A.; Lombardy, R. J.; Bentley, J. A.; Cory, M. Structure, DNA minor groove binding, and base pair specificity of alkyl and aryl linked bis(aminobenzimidazoles) and bis(amidinoindoles). *J. Med. Chem.* **1993**, *36*, 1746; (d) Heravi, M. M.; Sadjadi, S.; Oskooie, H. A.; Shoar, R. H.; Bamoharram, F. Heteropolyacids as heterogeneous and recyclable catalysts for the synthesis of benzimidazoles. *Catal. Commun.* **2008**, *9*, 504.

8. Brown, D. J. Quinoxalines: Supplements II. In *The Chemistry of Heterocyclic Compounds*; E. C. Tayler, P. Wipf (Eds.); John Wiley and Sons: NJ, 2004.
9. (a) Sylvain, A.; Elisabet, D. Direct and catalytic synthesis of quinoxaline derivatives from epoxides and ene-1,2-diamines. *Tetrahedron Lett.* **2002**, *43*, 3971 (b) Jose, B.; Fernando, A.; Romon, L.; Maria-Paz, C. One-pot synthesis of quinoxalines and 2,3-dihydropyrazines via oxidative aminomercuriation of propargyl alcohols. *Synthesis* **1985**, 313; (c) Steven, A. R.; Cecilia, D. W.; Richard, J. K. T. Preparation of quinoxalines, dihydropyrazines, and piperazines using tandem oxidation processes. *Chem. Commun.* **2003**, 2286; (d) Shyamaprasad, G.; Avijit, K. A. A novel one-pot two component synthesis of tricyclic pyrano[2,3*b*]quinoxalines. *Tetrahedron Lett.* **2005**, *46*, 221; (e) Yoram, C.; Amatzya, Y. M.; Mordecai, R. New polyheterocyclic 4n.pi-electron dianions: Paratropocity, charge delocalization, and reactions. *J. Am. Chem. Soc.* **1986**, *108*, 7039; (f) Xekoulotakis, N. P.; Hadjiantoniou, M.; Maroulis, A. J. Synthesis of quinoxalines by cyclization of α-arylamino oximes of α-dicarbonyl compounds. *Tetrahedron Lett.* **2000**, *41*, 10299; (g) Venu Gopal, K.; Subrahmanyam, M. Single-step synthesis of 2-methylquinoxaline from 1,2-phenylenediamine and 1,2-propanediol over modified HY zeolites. *Catal. Commun.* **2001**, *2*, 219.
10. (a) Shyamaprasad, G.; Avijit, K. A. The first microwave-assisted regiospecific synthesis of 6-substituted pterins. *Tetrahedron Lett.* **2002**, *43*, 8371; (b) Zhijian, Z.; David, D. W.; Scoot, E. W.; William, H. L.; Craig, W. L. General microwave-assisted protocols for the expedient synthesis of quinoxalines and heterocyclic pyrazines. *Tetrahedron Lett.* **2004**, *45*, 4873.
11. (a) Zemin, W.; Nicholas, J. E. Solid-phase synthesis of quinoxalines on Synphase$^{TM}$ lanterns. *Tetrahedron Lett.* **2001**, *42*, 8115 (b) Orazio, A. A.; Licia, D. C.; Paolino, F.; Fabio, M.; Stefania, S. Improved synthesis of substituted quinoxalines from new N = N-polymer-bound 1,2-diaza-1,3-butadienes. *Synlett* **2003**, 1183.
12. More, S. V.; Sastry, M. N. V.; Wang, C.-C.; Yao, C. Molecular iodine: A powerful catalyst for the easy and efficient synthesis of quinoxalines. *Tetrahedron Lett.* **2005**, *46*, 6345.
13. Darabi, H. R.; Mohandessi, S.; Aghapoor, K.; Mohsenzadeh, F. A recyclable and highly effective sulfamic acid/MeOH catalytic system for the synthesis of quinoxalines at room temperature. *Catal. Commun.* **2007**, *8*, 389.
14. (a) Shaabani, A.; Bazir, A.; Teimouri, F. Ammonium chloride-catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2-(1H)-ones under solvent-free conditions. *Tetrahedron Lett.* **2003**, *44*, 857 (b) Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. Halogenation of aromatic compounds by *N*-chloro, *N*-bromo, and *N*-iodosuccinimide. *Chem. Lett.* **2003**, *32*, 932.

15. (a) Gangadasu, B.; Narender, P.; Ramesh, C.; China Raju, B.; Rao, V. J. Facile and selective synthesis of chloronicotinaldehydes by the Vilmeier reaction. *Tetrahedron* **2006**, *62*, 8398 (b) China Raju, B.; Neelakantan, P.; Bhalerao, U. T. Quinone methide initiated cyclization reaction: Synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinolines. *Tetrahedron Lett.* **2004**, *45*, 7487 (c) Gangadasu, B.; China Raju, B.; Rao, V. J. A simple and convenient preparation of 2-chloro-5-methylpyridine-3-carbaldehydeimines. *Heterocycl. Commun.* **2002**, *8*, 243.
16. (a) Narender, P.; Gangadasu, B.; Ramesh, C.; China Raju, B.; Rao, V. J. Facile and selective synthesis of chloromethylpyridines and chloropyridines using diphosgene/triphosgene. *Synth. Commun.* **2004**, *34*, 1097 (b) Babu, K. S.; China Raju, B.; Srinivas, P. V.; Rao, J. M. Highly efficient and chemo selective cleavage of prenyl ethers using $ZrCl_4/NaBH_4$. *Tetrahedron Lett.* **2003**, *44*, 2525; (c) Babu, K. S.; China Raju, B.; Srinivas, P. V.; Rao, A. S.; Kumar, S. P.; Rao, J. M. A simple, effective, and highly selective cleavage of 3-methylbut-2-enyl(prenyl) ethers using p-toluenesulfonic acid. *Chem. Lett.* **2003**, *32*, 704.
17. Latif, N.; Mishriky, N.; Assad, F. M.; Meguid, S. B. β-Nitrostyrenes with *o*-phenylenediamine: A new route of the synthesis of 2-substituted benzimidazoles. *Indian J. Chem.* **1982**, *21B*, 872.
18. Bougrin, K.; Soufiaoui, M. Nouvelle voie de synthese des arylimidazoles sous irradiation micro-ondes en milieusec. *Tetrahedron Lett.* **1995**, *36*, 3683.
19. Matsushita, H.; Lee, S.-H.; Joung, M.; Clapham, B.; Janda, K. D. Smart cleavage reactions: The synthesis of benzimidazoles and benzothiazoles from polymer-bound esters. *Tetrahedron Lett.* **2004**, *45*, 313.
20. Kim, J. S.; Sun, Q.; Gatto, B. G.; Yu, C.; Liu, A.; Liu, L. F.; Lavoie, E. J. Structure-activity relationships of benzimidazoles and related heterocycles as topoisomerase I poisons. *Bioorg. Med. Chem.* **1996**, *4*, 621.
21. Valdez, J.; Cedillo, R.; Hernandez-Campos, A.; Yepez, L.; Hernandez-Luis, F.; Nararrete-Vazquez, G.; Tapia, A.; Cortes, R.; Hernandez, M.; Castillo, R. *Bioorg. Med. Chem Lett.* **2002**, *12*, 2221.
22. Mallory, F. B.; Wood, C. S.; Hurwitz, B. M. Furazan oxides IV: Extentions of the scope of the haloalkoxy substitution reaction. *J. Org. Chem.* **1964**, *29*, 2605.
23. Von Siegrist, A. E. Umberein neve synthese zur darstellung heterocyclish substituierter stilbene ver bindungen die anil-synthese. *Helvetica Chim. Acta* **1967**, *50*, 906.
24. Liu, J. H.; Wu, A. T.; Huang, M.-H.; Wu, C.-W.; Chung, W.-S. The synthesis of pyrazino-containing sultins and their application in Diels–Alder reactions with electron poor olefins and [60]fullerene. *J. Org. Chem.* **2000**, *65*, 3395.
25. Ainscow, T. A.; Belmont, M. R.; Henshall, J. L.; Hooper, R. M.; Simmonds, D. J. Synthesis of four n-alkanes with terminal dipolar substitutents. *Tetrahedron* **1987**, *43*, 115.
26. Kwon, H. B.; McKee, B. H.; Stille, J. K. Palladium-catalyzed coupling reactions of (alpha-ethoxyvinyl) trimethylstannane with vinyl and aryl triflates. *J. Org. Chem.* **1990**, *55*, 3114.