A Novel Palladium-Catalyzed Synthesis of 2-Arylbenzimidazoles

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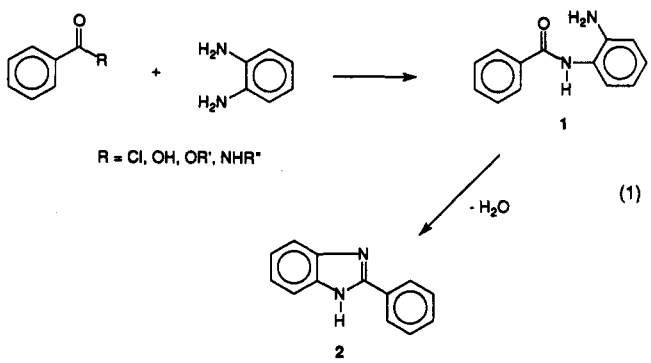
Received July 20, 1993•

A new method for the preparation of 2-arylbenzimidazoles based on the palladium-catalyzed carbonylation, coupling, and cyclization of haloaromatics and *o*-phenylenediamines is described. Reactions were run in DMAc at 145 °C for 18 h, under 95 psig CO, with 1.5 mol % $PdCl_2L_2$ as catalyst and in the presence of 1.2 equiv of 2,6-lutidine to give 70–98% yield of desired products. This route is tolerant of a variety of functional groups and nicely complements the classical route where the desired benzoic acid derivatives are unavailable. The selection of an appropriate base is crucial for the formation of 2-arylbenzimidazoles. Intermolecular bis-acylation to form bisamides occurs if the base is too strong. Weak bases allow side reactions with amide solvents to occur, leading to substituted benzamides and alkyl benzimidazoles.

Introduction

The benzimidazole nucleus is found in a variety of naturally occurring compounds such as vitamin B_{12} and its derivatives[1] and is also a key feature in cardiotonic agents such as pimobenden[2] and adibenden,[3] potential antitumor agents,[4] and antiulcer drugs.[5] This group also possesses great thermal stability and has been used as part of the backbone in high performance, high temperature polymers.[6] Traditional methods of 2-arylbenzimidazole synthesis involve the condensation and cyclization of benzoic acid (derivatives) and *o*-diamino aromatic compounds (eq 1).



1

2

(1)

The use of halogenated aromatics could offer an alternative route. Palladium-catalyzed carbonylations of aromatic halides and subsequent reactions with nucleophiles have been well documented for the formation of amides[7] and esters[8] as well as α-keto amides,[9] α-keto esters,[9e,10] α-keto acids,[11] α-hydroxy acids,[12] anhydrides,[13] acid fluorides,[14] acids,[15] lactams,[16] lactones,[17] aldehydes,[18] phthalimides,[19] and most recently benzoxazoles.[20] We have developed a new synthetic method for the preparation of 2-arylbenzimidazoles involving the palladium-catalyzed carbonylation, coupling, and cyclization of readily available aromatic halides and *o*-diaminobenzenes. Herein we report the results of our study.

Results and Discussion

We recently reported a method for the preparation of 2-arylbenzoxazoles involving the palladium-catalyzed carbonylation, coupling, and cyclization of aryl halides and *o*-aminophenols in the presence of a strong amine base like DBU.[20] Benzoxazole formation required a two-step

• Abstract published in *Advance ACS Abstracts*, November 1, 1993.

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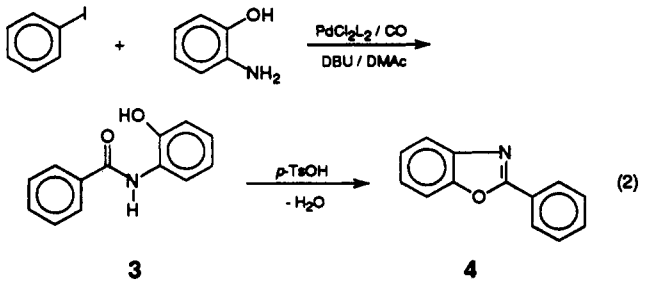
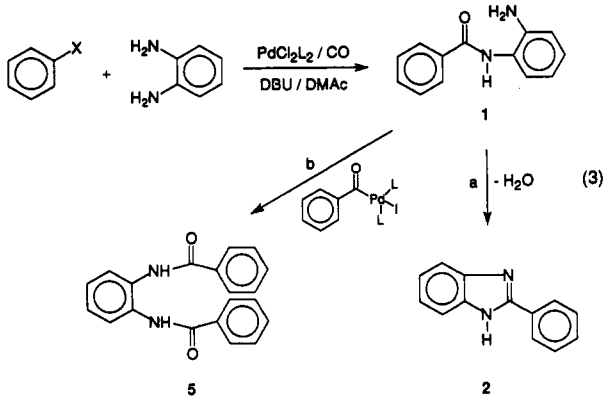
process in which the intermediate 2′-hydroxy-*N*-phenylbenzamide (3) was first formed and then, in a second step, cyclodehydrated with *p*-toluenesulfonic acid (*p*-TsOH) in refluxing toluene to give 4 (eq 2).



(2)

3 4

In the analogous reaction of *o*-diaminobenzene with iodobenzene, intermediate 1 was not detected and a nearly quantitative yield of bisamide 5 was isolated rather than the expected product 2 (eq 3). It was apparent that intermolecular attack of 1 on a palladium–acyl complex (path b) was favored over intramolecular cyclization (path a).



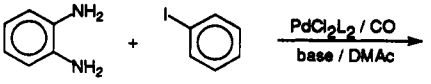
(3)

1 5 2

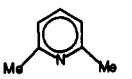
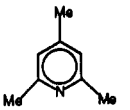
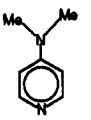
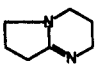
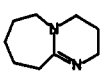
The use of a weaker base, such as 2,6-lutidine (Table I, entry c), suppressed bisamide formation and enhanced benzimidazole production. A series of bases were examined and it was observed that the stronger the base, the greater the amount of bisamide that was formed (Table I). This held true from the relatively weak base pyridine (pK_a = 5.2) through 6.5 orders of magnitude to the strongly basic amine DBU (pK_a = 11.9). The only exception to this was found to be tributylamine. A low yield of bisamide was formed but the reaction also produced other byproducts that were not identified. A comparably basic amine, DBN, was also tried and resulted in the clean formation of 83% bisamide. Base strength and not steric hindrance was crucial in suppressing bisamide formation as shown in the comparison of *s*-collidine and 2,6-lutidine. Both amines have pairs of adjacent methyl groups but the difference in undesired bisamide product is large.

Electron-deficient and electron-rich diamines were examined to determine if the base effect was a general one. Tables II and III reveal that the same trends were present in the methoxy- and chloro-substituted diamine systems, that is, that strong amine bases promoted bisamide formation and the weaker ones allowed intramolecular cyclization. When DABCO was used in the substituted diamine reactions, 60–80% bisamide formation occurred compared to only 33% in the parent system. This may indicate a greater sensitivity of the substituted diamines to the effect of strong base.

Table I. Effect of Base on Bisamide Formation for Parent System[a]



2 5

entry	base	structure	pK_a[22]	% bisamide[b]
a	pyridine		5.2	2
b	4-picoline		6.0	2
c	2,6-lutidine		6.6	2
d	*s*-collidine		7.4	12
e	*N*-methylmorpholine		7.5	19
f	DABCO		8.2	33
g	DMAP		9.7	83
h	tributylamine		10.9	28
i	DBN		11.0	83
j	DBU		11.9	95

[a] Reaction in DMAc (0.3 M), 140 °C, 95 psig CO, 1.5% $PdCl_2L_2$, 1.2 equiv of base, 24 h. [b] GC yield.

To more fully explore the reason for the base effect, the reaction intermediate 2-aminobenzanilide (1) was prepared and subjected to a variety of cyclization conditions. In the presence of 2,6-lutidine in *N*,*N*-dimethylacetamide (DMAc) at 140 °C, less than 20% cyclization to benzimidazole 2 had occurred in 24 h while 50% cyclization was seen in the presence of DBU (Table IV). This is consistent with the fact that a stronger base promotes cyclization at a faster rate than a weaker base.[21] However, these observed rates were much slower than those seen during the actual reaction where nearly quantitative yields of benzimidazoles were formed in less than 24 h. It has been shown that acid-catalyzed cyclization of *o*-amino-*N*-substituted amides is more effective by a factor of 5000.[21] In our synthesis we generate HI, which is then neutralized by the base. But, the equilibrium concentration of acid present from B·HI ⇌ B + HI will be much greater in the case of 2,6-

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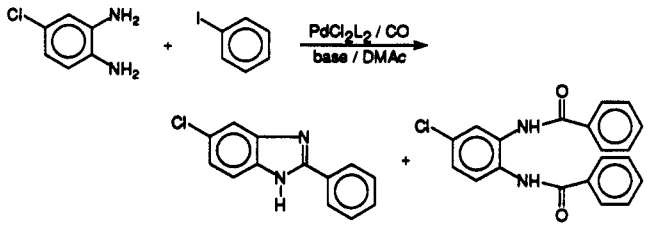
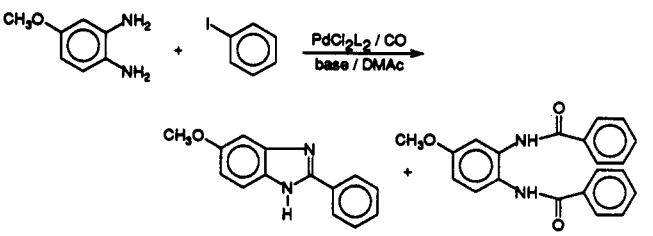
Table II. Effect of Base on Bisamide Formation from 4-Chloro-o-phenylenediamine[a]



entry	base	pK_a[22]	% bisamide[b]
a	pyridine	5.2	2
b	3-picoline	5.7	4
c	4-picoline	6.0	4
d	2,6-lutidine	6.6	8
e	*N*-methylmorpholine	7.6	24
f	DABCO	8.2	80

[a] Reaction in DMAc (0.3 M), 140 °C, 95 psig CO, 1.5% $PdCl_2L_2$, 1.2 equiv of base, 24 h. [b] GC yield.

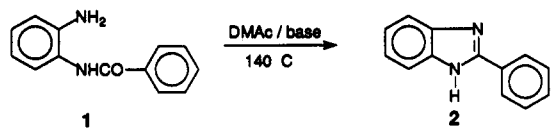
Table III. Effect of Base on Bisamide Formation from 4-Methoxy-o-phenylenediamine[a]



entry	base	pK_a[22]	% bisamide[b]
a	pyridine	5.2	2
b	3-picoline	5.7	2
c	4-picoline	6.0	4
d	2,6-lutidine	6.6	7
e	DABCO	8.2	57

[a] Reaction in DMAc (0.3 M), 140 °C, 95 psig CO, 1.5% $PdCl_2L_2$, 1.2 equiv of base, 24 h. [b] GC yield.

Table IV. Cyclization of 1 → 2[a]



1 2

base	time (h)	% 2
2,6-lutidine	24	18
DBU	24	50
2,6-lutidiene·HCl	1	100
DBU·HCl	7	4

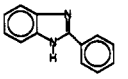
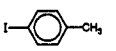
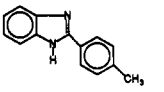
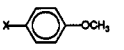
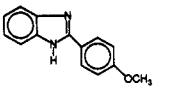
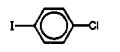
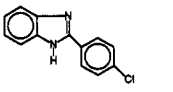
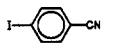
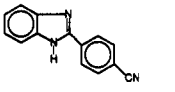
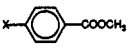
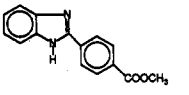
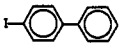
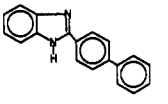
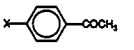
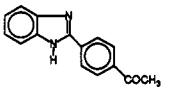
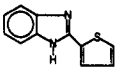
[a] Reaction in DMAc (0.3 M), 140 °C, 1.2 of equiv base.

lutidine than DBU owing to its less basic nature. Treating 1 with 2,6-lutidine hydroiodide under conditions described above resulted in complete cyclization to **2** in less than 1 h. The corresponding DBU·HI salt showed only 4% formation of benzimidazole in 7 h. It appears that the cyclization is acid-catalyzed even in the presence of excess base.

To see if the catalyst also participated in the ring closure reaction, 1 was treated with $PdCl_2L_2$. After 1 h, a small amount of cyclization had occurred (18%). Portions of the solution were then treated with 2,6-lutidine and DBU. The lutidine reaction showed 37% cyclization in 7 h whereas the DBU reaction showed only 20% in the same time.

Believing that this difference might be due to formation of small amounts of HCl from the catalyst, $Pd(PPh_3)_4$ was then used. The same set of reaction conditions with $Pd(PPh_3)_4$ showed only 10% cyclization after 7 h in the presence of 2,6-lutidine in comparison to 21% with DBU. Cyclization with the catalyst and no added base occurred to give 20% ring closure. This suggests that the small amount of HCl produced from $PdCl_2L_2$ did have a small positive effect in the cyclization reaction.

Table V. Reaction of o-Phenylenediamine with Substituted Haloaromatics[a]

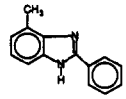
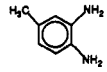
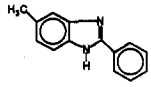
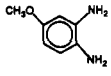
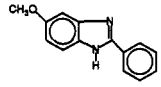
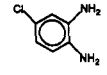
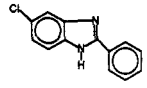
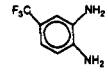
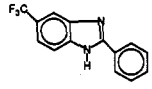
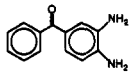
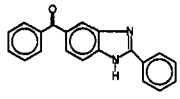
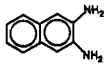
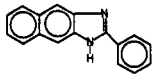
entry	haloaromatic	benzimidazole **2**	yield (%)[b]	
a				75
b				81
c			X = I X = Br	71 68
d				93
e				74
f			X = I X = Br	60 76
g				75
h			X = I X = Br	92 81
i				38

[a] Reaction in DMAc (0.3 M), 140 °C, 95 psig CO, 1.5% $PdCl_2L_2$, 1.2 equiv of 2,6-lutidine, 24 h. [b] Yields are for isolated, purified products.

Using 2,6-lutidine as the base, the most favorable conditions found for benzimidazole formation in the parent system were 1.5 mol % catalyst as $PdCl_2L_2$, DMAc as the solvent, 95 psig CO, and a reaction temperature of 140–145 °C. Having at least partially optimized the parent system, we wished to determine the scope of the reaction. Table V shows the variety of functional groups tolerated on the haloaromatic moiety. Good to excellent yields of benzimidazoles were obtained from aromatics with electron-donating groups, such as methyl **2b** and methoxy **2c**, as well as electron-withdrawing ones like chloro **2d**, cyano **2e**, acetyl **2h**, and carbomethoxy **2f**. 2-Iodothiophene was the only substrate that gave a modest yield of the desired benzimidazole. The reason for this is unclear at this time although several other byproducts were seen by GC.

Changing from iodoaromatics to bromoaromatics posed no problem. As can be seen from Table V, comparable yields of benzimidazoles were obtained from analogous iodo and bromo derivatives. In the methoxy case, **2c**, the yields were essentially the same. For ester **2f**, the bromo derivative gave a 16% higher isolated yield than the iodo

Table VI. Reaction of Iodobenzene with Substituted *o*-Phenylenediamines[a]

entry	diamine	benzimidazole 2	yield (%)[b]
j			98
k			94
l			95
m			91[b,c]
n			97
o			89
p			77

[a] Reaction in DMAc (0.3 M), 140 °C, 95 psig CO, 1.5% $PdCl_2L_2$, 1.2 equiv of 2,6-lutidine, 24 h. [b] Yields are for isolated, purified products. [c] 8% of the bisamide was also isolated.

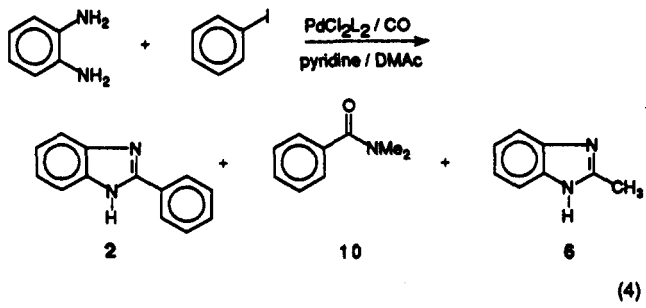
compound. In contrast, the electron-withdrawing acetyl group, **2h**, gave an 11% greater yield from the iodo derivative.

The yields are likewise excellent for benzimidazoles made from substituted *o*-phenylenediamines (Table VI). Electron-donating substituents gave isolated yields of products **2j–l** in excess of 94%. Electron-withdrawing groups also gave excellent yields from 89% with the benzoyl group **2o** to 97% for the trifluoromethyl group **2n**. The chloro derivative **2m** gave a 91% yield of product but also 8% of the bisamide.

In most cases with *o*-phenylenediamine and haloaromatics (Table V), less than 3% bisamide was observed by GC. We had shown that decreasing the base strength in the parent system (Table I) lessened the amount of bisamide formed. Decreasing the base strength might further diminish the bisamide content in the chlorophenylenediamine. Initially we had not examined bases weaker than 2,6-lutidine in these reactions and so looked at their effect in the parent system and in the chloro- and methoxy-substituted systems.

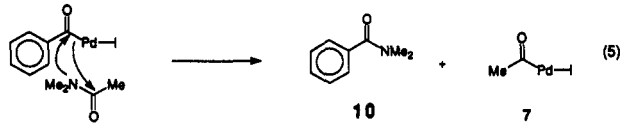
We found that going from 2,6-lutidine (pK_a = 6.6) to 4-picoline (pK_a = 6.0) decreased the bisamide content of the chloro system from 8% to 4%. Weaker bases like 3-picoline (pK_a = 5.7) and pyridine (pK_a = 5.2) had little further effect on bisamide formation. The same held true for the methoxy and parent cases as well. What was noted, though, was that benzimidazole production was also suppressed. In its place, two other materials were formed in large amounts. In the parent system these were identified as **10** and **6** (eq 4).

These materials arose from reaction of solvent fragments from palladium-assisted solvent dissociation. *N,N*-Dimethylbenzamide (**10**) could form from a palladium–acyl intermediate and a dimethylamino transfer from DMAc



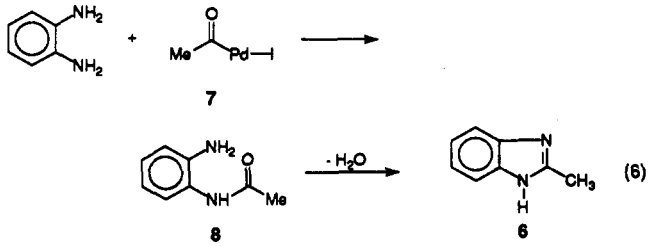
(4)

in an acyl exchange reaction (eq 5). The acetylpalladium



(5)

species **7** could also then react with *o*-phenylenediamine, followed by cyclization (eq 6).

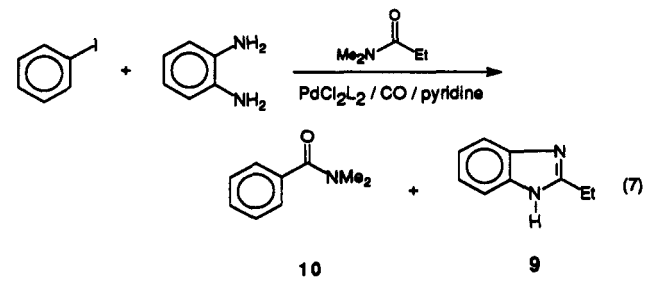


(6)

Control experiments indicated palladium was necessary for these reactions to occur. Neither product was formed in its absence. If the diamine was omitted, *N,N*-dimethylbenzamide (**10**) still formed although 2-methylbenzimidazole (**6**) did not. Analogously, the absence of iodobenzene did not permit the formation of **10** but **6** was still produced.

When the solvent was changed to chlorobenzene, a solvent unable to undergo dissociation, these side products were not observed. Instead, a 73% yield of the benzimidazole **2** was isolated. Although a good yield of product could be obtained in this solvent, the reaction mixture was biphasic and the yield was not as high as in the optimized DMAc system.

Further evidence for palladium-assisted solvent decomposition and transacylation came from a reaction performed in *N,N*-dimethylpropionamide (DMPa). The reaction of iodobenzene, *o*-phenylenediamine, $PdCl_2L_2$, and CO in DMPa gave *N,N*-dimethylbenzamide (**10**) and 2-ethylbenzimidazole (**9**) (eq 7).



(7)

Conclusions

The formation of 2-arylbenzimidazoles can be accomplished in high yield through the palladium-catalyzed

carbonylation, coupling, and cyclization of haloaromatics and *o*-phenylenediamines. This route is tolerant of a variety of functional groups and nicely compliments existing routes where the desired benzoic acid derivatives are unavailable. The selection of an appropriate base is crucial for the clean, high yield formation of 2-arylbenzimidazoles. Intermolecular bisacylation to form bisamides predominates if the base is too strong. On the other hand, a weak base allows side reactions with amide solvents leading to substituted benzamides and unwanted benzimidazoles.

Experimental Section

General Procedures. Reactions were performed in a 120-mL pressure reaction vessel (containing a stir bar) from Aerosol Laboratory Equipment Corp. fitted with a pressure gauge, a pressure release valve, a gas inlet, and a straight ball valve for degassing and sample withdrawal. All reactions were run at 0.3 M in *N,N*-dimethylacetamide (DMAc) at 140–145 °C under 95 psig CO using 1.5% $PdCl_2L_2$ as the catalyst system unless otherwise noted.

All reactions were monitored on an HP 5890 gas chromatograph using a 15-m, 0.25-μm DB-5 column (0.32 mm i.d.) and a flame ionization detector. Helium flow rate through the column was 4.0 mL/min. The GC parameters employed for analysis were as follows: injection port, 300 °C; detector, 350 °C; temperature ramp from 50 °C (hold 1 min) to 300 °C (hold 10 min) at 20 °C/min. Electron ionization (EI) mass spectral data were obtained at 70 eV on an HP 5987A GC/MS. The instrument had been modified with a 5988A interface, which allows the GC column to be brought directly into the mass spectrometer source. The GC parameters employed for analysis were as follows: a J & W 15-m, 0.25-μm DB-5 column (0.32 mm i.d.); injection port, 250 °C; transfer line, 325 °C; source, 200 °C; temperature ramp from 50 °C to 300 °C at 20 °C/min. ^1H NMR and ^{13}C NMR spectra were recorded on a General Electric QE-300 (300 MHz) spectrometer using $CDCl_3$ or DMSO-d_6 as both internal standard and solvent. Fourier transform infrared spectra were recorded on a Nicolet 60SX spectrometer as KBr pellets. Chromatography was performed using Woelm silica gel, 60–200 mesh. Elemental analyses were performed by the Analytical Technology Division of Eastman Kodak Company.

Iodobenzene, 4-iodotoluene, 4-iodoanisole, 4-bromoanisole, 4-iodobenzonitrile, 4-iodobenzoic acid, 4-bromobenzoic acid, 2-iodothiophene, 4′-iodoacetophenone, 4′-bromoacetophenone, 2,6-dimethylpyridine (2,6-lutidine), 4-(dimethylamino)pyridine (DMAP), 2,4,6-trimethylpyridine (*s*-collidine), 1,4-diazabicyclo-[2.2.2]octane (DABCO), pyridine (all Kodak), 1-chloro-4-iodobenzene, 2,3-diaminotoluene, 3,4-diaminotoluene, 4-chloro-1,2-diaminobenzne, 3,4-diaminobenzophenone, 2,3-diaminonaphthalene, 4-methoxy-1,2-diaminobenzene, *N,N*-diethylacetamide, *N,N*-dimethylpropionamide, *N,N*-dimethylacetamide (anhydrous), bis(triphenylphosphine)palladium(II) chloride ($PdCl_2L_2$) (all Aldrich, CO (Air Products, UPC grade), and 4-(trifluoromethyl)-1,2-diaminobenzene (Maybridge) were all used as received. Triphenylphosphine was recrystallized from hexanes, 4-iodobiphenyl (Kodak) was recrystallized from ethanol, 1,2-diaminobenzene (Kodak) was recrystallized from water and then 2-propanol, DBU (Aldrich) was fractionally distilled under reduced pressure, and toluene was distilled from sodium/benzophenone ketyl.

Detailed Example. Preparation of 2-Phenylbenzimidazole (2a). A pressure reaction vessel was charged with *o*-diaminobenzene (967 mg, 8.94 mmol), iodobenzene (1.00 mL, 8.94 mmol), $PdCl_2L_2$ (94 mg, 0.13 mmol), and DMAc (27 mL). The contents were deoxygenated with argon then placed under 35 psig CO and stirred at 120 °C until all reagents had dissolved. Then the pressure was released and 2,6-lutidine (1.40 mL, 12.0 mmol) was added by syringe through the ball valve. The reactor was charged to 95 psig CO and stirred for 19 h at 145 °C. The reaction mixture was filtered through filter-aid to remove palladium and then concentrated in vacuo. The residue was dissolved in hot water, filtered hot, cooled and the product was collected as off-white crystals. The product was then slurried in water/ammonium hydroxide solution, filtered, dried in air, and recrystallized from ethanol/water to give 1.30 g product (75 %): mp 289–291 °C (lit.[23] mp 295 °C). ^1H NMR ($CDCl_3$): δ 7.94 (dd, J = 7.8, 1.3 Hz, 2), 7.48 (m, 1), 7.22 (m, 4), 6.96 (m, 2).

***N,N*-Dibenzoyl-*o*-phenylenediamine (3).** As described above *o*-diaminobenzene (967 mg, 8.94 mmol), iodobenzene (1.00 mL, 8.94 mmol), $PdCl_2L_2$ (94 mg, 0.13 mmol), DBU (1.60 mL, 10.7 mmol), and DMAc (27 mL) were allowed to react under 95 psig at 145 °C for 2.5 h. The reaction mixture was filtered and the bisamide product was collected at 1.37 g (96%) off-white crystals: mp 285–286 °C (lit.[24] mp 305 °C). Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.85. Found: C, 75.88; H, 5.12; N, 8.77.

2-(4-Methylphenyl)benzimidazole (2b). After concentrating the filtrate, the residue was recrystallized from 50% aqueous acetic acid then slurried in water/ammonium hydroxide solution, filtered, dried in air, and recrystallized from ethanol/water to give 1.50 g product (81%): mp 270–272 °C (lit.[25] mp 275–276 °C). ^1H NMR (DMSO-d_6): δ 12.80 (br s, 1), 8.05 (d, J = 8.0 Hz, 2), 7.56 (m, 2), 7.32 (d, J = 8.0 Hz, 2), 7.16 (m, 2), 2.33 (s, 3).

2-(4-Methoxyphenyl)benzimidazole (2c). After concentrating the filtrate, the residue was dissolved in 45 mL of hot aqueous ethanol then allowed to cool. The solid crystalline product was redissolved in hot ethanol, treated with 3 mL of NH_4OH, diluted with water, and cooled. The product was collected as a colorless solid: 1.42 g (71%); mp 222–225 °C (lit.[25] mp 226–227 °C). ^1H NMR ($CDCl_3$): δ 8.08 (d, J = 8.8 Hz, 2), 7.74 (m, 2), 7.48 (m, 2), 7.24 (d, J = 8.8 Hz, 2), 3.84 (s, 3).

2-(4-Chlorophenyl)benzimidazole (2d). After concentrating the filtrate, the residue was recrystallized from 50% aqueous acetic acid to give 2.09 g of product. This was then slurried in water/ammonium hydroxide solution, filtered, dried in air, and recrystallized from ethanol/water to give 1.90 g product (93%): mp 290–292 °C (lit.[23] mp 303 °C). ^1H NMR (DMSO-d_6): δ 12.98 (br s, 1), 8.18 (d, J = 8.4 Hz, 2), 7.58 (d, J = 8.4 Hz, 2), 7.57 (m, 2), 7.19 (m, 2).

2-(4-Cyanophenyl)benzimidazole (2e). After concentrating the filtrate, the residue was recrystallized from 50% aqueous acetic acid, slurried in water/ammonium hydroxide solution, filtered, dried in air, and recrystallized from ethanol/water to give 1.45 g product (74%): mp 261–262 °C (lit.[26] mp 262.5 °C). ^1H NMR (DMSO-d_6): δ 13.17 (br s, 1), 8.30 (d, J = 8.4 Hz, 2), 7.95 (d, J = 8.2 Hz, 2), 7.61 (br s, 2), 7.21 (m, 2).

2-(4-Carbomethoxyphenyl)benzimidazole (2f). After concentrating the filtrate, the residue was dissolved in 10 mL of warm methanol and treated with 1 mL of NH_4OH and then 10 mL water. The solution was warmed to effect dissolution and then cooled. The crystalline solid was collected, washed with cold methanol/water, and dried to give 541 mg (60%) product as colorless crystals: mp 220–222 °C. ^1H NMR (DMSO-d_6): δ 8.28 (d, J = 8.0 Hz, 2), 8.07 (d, J = 8.0 Hz, 2), 7.59 (m, 2), 7.21 (m, 2), 3.84 (s, 3). Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.62; H, 4.83; N, 11.19.

2-(4-Biphenyl)benzimidazole (2g). After concentrating the filtrate, the residue was dissolved in 75 mL hot ethanol and treated with 2 mL of NH_4OH and then 25 mL of water. The solution was cooled. The crystalline solid was collected, washed with cold ethanol/water, and dried to give 2.296 g (95%) of product as colorless crystals: mp 294–296 °C (lit.[27] mp 303–305 °C). ^1H NMR (DMSO-d_6): δ 8.28 (d, J = 8.2 Hz, 2), 7.84 (d, J = 8.2 Hz, 2), 7.72 (d, J = 7.5 Hz, 2), 7.12 (br s, 2), 7.45 (t, J = 7.4 Hz, 2), 7.36 (d, J = 7.1 Hz, 1), 7.20 (m, 2).

2-(4-Acetylphenyl)benzimidazole (2h). After concentrating the filtrate, the residue was dissolved in 25 mL of hot ethanol

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(27) Seiler, J. P.; Limacher, H. *Chimia* **1973**, *27*, 68.

and treated with 3 mL of NH_4OH and then 25 mL of water. The solution was cooled. The solid was collected, washed with cold ethanol/water, and dried to give 718 mg (34%) product. The filtrate was concentrated and then filtered through a plug of silica gel, eluting with 1:1 toluene:EtOAc to give 1.225 g (58%) of product. A small sample was sublimed at 190 °C/0.11 Torr to give mp 228–232 °C. ^1H NMR (DMSO-d_6): δ 12.7 (br s, 1), 8.13 (d, J = 7.9 Hz, 2), 7.4 (m, 4), 7.08 (br s, 1), 6.82 (dd, J = 8.7, 2.0 Hz, 1), 3.78 (s, 3). Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.19; H, 5.12; N, 11.91.

2-(2-Thienyl)benzimidazole (2i). After concentrating the filtrate, the residue was dissolved in 25 mL of hot ethanol and treated with 2 mL of NH_4OH and then 25 mL of water. The solution was cooled overnight. The solid was collected and washed with cold ethanol/water and dried to give 588 mg (32%) of product. The filtrate was concentrated and then filtered through a plug of silica gel, eluting with 1:1 toluene:EtOAc to give another 104 mg (6%) product: mp 332–334 °C (lit.[25] mp 332–334 °C). ^1H NMR (DMSO-d_6): δ 13.0 (br s, 1), 7.83 (d, J = 3.4 Hz, 1), 7.68 (d, J = 4.9 Hz, 1), 7.55 (br s, 2), 7.18 (m, 3).

4-Methyl-2-phenylbenzimidazole (2j). After concentrating the filtrate, the residue was dissolved in hot 50% aqueous methanol and then treated with 1 mL of NH_4OH. The solid was isolated, washed with cold solvent mixture, and recrystallized from aqueous methanol to give 1.816 g (98%) of product as light brown crystals: mp 248–249 °C (lit.[28] mp 246–247 °C). ^1H NMR (DMSO-d_6): δ 8.21 (br s, 2), 7.51 (m, 4), 7.07 (t, J = 7.5 Hz, 1), 6.96 (d, J = 7.1 Hz, 1), 2.56 (s, 3).

5-Methyl-2-phenylbenzimidazole (2k). After concentrating the filtrate, the residue was dissolved in 25 mL of hot ethanol and then treated with 2 mL of NH_4OH and then 25 mL of water. The mixture was heated and after cooling, the solid was isolated and washed with cold solvent mixture and then recrystallized twice from aqueous ethanol to give 1.30 g (70%) of product as off-white crystals. An additional 440 mg (24%) product was isolated from the filtrate: mp 242–243 °C (lit.[28] mp 241–242 °C). ^1H NMR (DMSO-d_6): δ 12.7 (br s, 1), 8.15 (d, J = 7.5 Hz, 2), 7.48 (m, 4), 7.36 (s, 1), 6.99 (d, J = 8.2 Hz, 1), 2.40 (s, 3).

5-Methoxy-2-phenylbenzimidazole (2l). After concentrating the filtrate, the residue was dissolved in 25 mL of hot ethanol and then treated with 2 mL of NH_4OH. The mixture was concentrated, dissolved in a mixture of toluene/EtOAc, and passed through a short column of silica gel, eluting with the same solvent mixture to give 1.91 g (92%) of product. The solid was isolated and recrystallized twice from ether to give colorless crystals: mp 143–144 °C (lit.[29] mp 147 °C). ^1H NMR (DMSO-d_6): δ 12.7 (br s, 1), 8.13 (d, J = 7.9 Hz, 2), 7.4 (m, 4), 7.08 (br s, 1), 6.82 (dd, J = 8.7, 2.0 Hz, 1), 3.78 (s, 3). The solid removed on filtering was N,N'-dibenzoyl-1,2-diamino-4-methoxybenzene: mp 249–251 °C. ^1H NMR (DMSO-d_6): δ 10.01 (s, 1), 9.96 (s, 1), 7.92 (m, 4), 7.51 (m, 7), 7.32 (d, J = 2.4 Hz, 1), 6.86 (dd, J = 8.8, 2.4, Hz, 1), 3.77 (s, 3).

5-Chloro-2-phenylbenzimidazole (2m). After concentrating the filtrate, the residue was dissolved in 25 mL of hot ethanol and then treated with 3 mL of NH_4OH and then 25 mL of water. The mixture was heated and filtered hot. The insoluble material (275 mg) was found to be the bisamide derivative N,N'-dibenzoyl-1,2-diamino-4-chlorobenzene: mp 218–221 °C. ^1H NMR (DMSO-d_6): δ 10.08 (s, 2), 7.92 (m, 4), 7.77 (d, J = 1.7 Hz, 1), 7.65 (d, J = 8.6 Hz, 1), 7.5 (m, 6), 7.32 (dd, J = 8.6, 1.7 Hz, 1). The desired product was collected after cooling to give 1.86 g (91%) of light brown crystals: mp 206–210 °C after sublimation at 185 °C/0.05 Torr (lit.[28] mp 209–210 °C. ^1H NMR (DMSO-d_6): δ 12.8 (br s, 1), 8.18 (d, J = 7.2 Hz, 2), 7.5 (m, 5), 7.19 (dd, J = 8.2, 1.0 Hz, 1).

5-(Trifluoromethyl)-2-phenylbenzimidazole (2n). After concentrating the filtrate, the residue was dissolved in 25 mL of hot ethanol and then treated with 3 mL of NH_4OH and then 25 mL of water. The mixture was heated and cooled. The oil formed on cooling eventually crystallized. The solid was dissolved in 1:1 toluene:EtOAc and passed through a short column of silica gel, eluting with 4:1 toluene:EtOAc. The crude product was sublimed at 175 °C/0.13 Torr and passed through another pad of silica gel, eluting with 1:1 toluene:EtOAc to give 1.14 g (97%) product as a colorless solid: mp 191–192 °C (lit.[30] mp 195–196 °C). ^1H NMR (DMSO-d_6): δ 13.4 (br s, 1), 8.19 (d, J = 7.3 Hz, 1), 7.93 (s, 1), 7.75 (d, J = 7.3 Hz, 1), 7.5 (m, 4).

5-Benzoyl-2-phenylbenzimidazole (2o). After concentrating the filtrate, the residue was dissolved in 25 mL of hot ethanol and then treated with 3 mL of NH_4OH and then 25 mL of water. The mixture was heated and then cooled to give 2.38 g (89%) of product as light brown crystals: mp 221–221.5 °C after recrystallization from aqueous ethanol. ^1H NMR (DMSO-d_6): δ 13.3 (br s, 1), 8.19 (d, J = 7.9 Hz, 2), 7.95 (br s, 1), 7.7 (m, 5) 7.5 (m, 5). Anal. Calcd for $C_{20}H_{14}N_2O$: C, 80.52; H, 4.73; N, 9.39. Found: C, 80.62; H, 4.83; N, 9.29.

2-Phenylnaphthimidazole (2p). After concentrating the filtrate, the residue was recrystallized from 50% aqueous acetic acid; slurried in water/ammonium hydroxide solution, filtered, dried in air, and recrystallized from ethanol/water to give 1.67 g of product (77%): mp 210–212 °C (lit.[28] mp 213–214 °C). ^1H NMR (DMSO-d_6): δ 12.96 (br s, 1), 8.27 (d, J = 6.7 Hz, 2), 8.09 (m, 2), 7.98 (m, 2), 7.55 (m, 3), 7.34 (m, 2).

2′-Aminobenzanilide (1). This compound was prepared by the Raney nickel hydrogenation of 2′-nitrobenzanilide which was prepared from the reaction of 2-nitroaniline and benzoyl chloride: mp 150–152 °C (lit.[31] mp 148–151 °C). ^{H} NMR (DMSO-d_6): δ 9.66 (br s, 1), 7.96 (d, J = 7.2 Hz, 2), 7.51 (m, 3), 7.15 (d, J = 7.6 Hz, 1), 6.95 (t, J = 7.0 Hz, 1), 6.77 (d, J = 8.0 Hz, 1), 6.58 (7, J = 7.3 Hz, 1), 4.89 (br s, 2).

Mass Spectral Data on Unisolated Products. *N,N*-Dimethylbenzamide (10): m/z (relative intensity) 150 (2), 149 (21), 148 (65), 106 (8), 105 (100), 77 (54), 51 (15), 50 (6).

2-Methylbenzimidazole (6): m/z (relative intensity) 133 (9), 132 (100), 131 (80), 104 (10), 92 (6), 90 (9), 77 (9), 65 (11), 64 (14), 63 (21), 62 (8), 52 (10), 51 (8), 42 (6), 39 (10), 38 (7), 28 (10).

2-Ethylbenzimidazole (7): m/z (relative intensity) 147 (5), 146 (55), 145 (100), 131 (17), 119 (4), 118 (8), 104 (4), 92 (5), 91 (4), 77 (5), 65 (4), 64 (4), 63 (6).

Acknowledgment. We wish to thank J. Lugert for GC/MS results and P. Keogh for help in their interpretation.

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