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An Improved Procedure for the Synthesis of Benzimidazoles, Using Palladium-Catalyzed Aryl-Amination Chemistry

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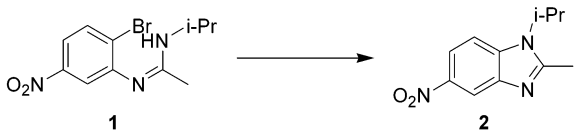
Abstract: New, improved conditions have been developed and optimized for the synthesis of benzimidazoles by intramolecular palladium-catalyzed aryl-amination chemistry. This methodology, combined with a "catch and release" purification strategy, has led to a range of these heterocycles being prepared rapidly and in excellent yield.

Over the past few years much effort has gone into developing palladium-catalyzed aryl-amination chemistry.[1] The initial work by both Buchwald and Hartwig focused on intermolecular aminations of aryl bromides and iodides to give substituted anilines.[2] More recently, this aryl-amination chemistry has undergone optimization, particularly with the development of new ligand systems.[3] Having established this chemistry it was rapidly applied in an intramolecular sense to the synthesis of heterocyclic compounds.[4] As a result, this chemistry has been utilized in the synthesis of indoles and derivatives,[5] phenazines,[6] indazoles,[7] benzazepines,[8] aminobenzimidazoles,[9] and other heterocyclic compounds.[10]

Previously we reported the preliminary results of a novel benzimidazole[11] synthesis (e.g. Scheme 1).[12] We were eager to optimize this methodology by addressing various issues, specifically the high catalytic loading, the apparent necessity of the NaO*t*-Bu/K_2CO_3 base system,[4] and last the difficulty of separating the benzimidazoles from phosphine residues. Additionally, we were interested in determining whether the benzimidazole synthesis could be made amenable to a high-throughput protocol by having short reaction times (possibly with the use of microwave heating[13]) and by using nonchromatographic purification techniques.

SCHEME 1[a]



[a] Reagents and conditions: 5−10 mol % of $Pd(PPh_3)_4$, 1.6 equiv of NaO*t*-Bu, 1.6 equiv of K_2CO_3, PhMe, reflux, 18 h, 91%.

Amidine **1** was chosen as the substrate on which to carry out the optimization since it is activated toward oxidative addition. Initially, we investigated the base system: Buchwald's NaO*t*-Bu/K_2CO_3 base mixture was replaced with NaOH. With this base the reaction proceeded, albeit very slowly (incomplete conversion after reflux for 40 h). Surmising that the slow reaction rate was due to the poor solubility of NaOH in toluene caused us to attempt aqueous reaction conditions (20% water/xylene).[14] This led to complete conversion of amidine **1** to benzimidazole **2** after 2 h at reflux. We were encouraged by this result as it demonstrated the applicability of aqueous conditions in palladium-catalyzed aryl-amination chemistry.[15−17] This chemistry was then attempted with microwave heating:[18] a quantitative conversion to benzimidazole **2** occurred in just 20 min at 200 °C, with

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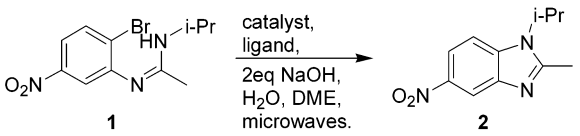
TABLE 1. Palladium-Catalyzed Intramolecular Amination of Amidine 1 to Benzimidazole 2: Effect of Catalyst, Stoichiometry of Palladium to Ligand, Solvent Ratio, and Concentration



1 **2**

entry	catalyst	mol % of Pd	ligand	mol % of ligand	% of water[a]	concn of amidine/M	temp/ °C	time/ min	conversion[b]/ %
1	$Pd(PPh_3)_4$	10			20[c]	0.034	200	20	>98
2	$Pd(PPh_3)_4$	10			13	0.034	150	8	>98
3	$Pd(PPh_3)_4$	5			13	0.034	150	9	>98
4	$Pd(PPh_3)_4$	2			13	0.034	185	50	83
5	$Pd_2(dba)_3$	10	PPh_3	10	13	0.034	150	25	>98
6	$Pd_2(dba)_3$	5	PPh_3	5	13	0.034	150	33	67
7	$Pd_2(dba)_3$	5	PPh_3	5	13	0.034	130	33	>98
8	$Pd_2(dba)_3$	5	PPh_3	5	15	0.065	130	83	87
9	$Pd_2(dba)_3$	5	PPh_3	5	25	0.065	130	17	>98
10	$Pd_2(dba)_3$	1	PPh_3	1	25	0.065	130	42	20
11	$Pd_2(dba)_3$	1	PPh_3	2	25	0.065	130	42	63
12	$Pd_2(dba)_3$	1	PPh_3	4	25	0.065	130	10	>98
13	$Pd_2(dba)_3$	1	PPh_3	4	25	0.065	160	5	>98

[a] The percentage water in a water/DME mixture. [b] Conversions were determined by ^{1}H NMR. [c] This reaction was carried out in a 20% water/xylene solution with 10 mol % of *n*-Bu_4NOH.

the addition of 10 mol % of *n*-Bu_4NOH as a phase transfer catalyst (Table 1, entry 1).

Having established these aqueous reaction conditions, we wanted to further optimize the reaction by varying other parameters: the solvent system, catalytic loading, palladium source, stoichiometry of palladium to ligand, and concentration (Table 1).

Initially, we studied the effect of the organic solvent on the reaction. Solvents were chosen that were miscible with water with a view to eliminating the need for the phase transfer reagent. Thus, experiments were carried out with diglyme, dioxane, and DME, all without *n*-Bu_4NOH. In each case the amination proceeded well, but DME was found to be the optimal solvent. Indeed it proved to be superior to xylene as the reaction time and temperature were both reduced (Table 1, entries 1 and 2).

It was found that the amount of palladium could be readily reduced to 5 mol %, but when it was lowered to 2 mol % incomplete conversions were achieved, despite using longer reaction times and higher temperatures (Table 1, entries 2−4).

The use of $Pd_2(dba)_3$ was then investigated (Table 1, entries 5 and 6). Using 10 and 5 mol % of Pd respectively led to a less efficient process compared with that with $Pd(PPh_3)_4$ (Table 1, compare entries 5 and 6 with entries 2 and 3).

Increasing the concentration with respect to the amidine (Table 1, entry 8 compared to entry 7) surprisingly lengthened the time required for the reaction to occur. However, it was found that the ratio of water to DME had a dramatic effect on the reaction rate and that increasing the proportion of water from 15% to 25% caused the reaction to proceed more rapidly than had been previously seen with this catalyst (Table 1, entries 8 and 9).

When the ratio of palladium to ligand was varied from 1:1 to 1:2 and 1:4 (Table 1, entries 10−12) the reaction time decreased significantly. Interestingly the reaction was most rapid when the ratio was 1:4.[19] Finally, the temperature that the reaction could be carried out at was optimized (Table 1, entry 13): 160 °C was the maximum operating temperature without palladium metal precipitating from the reaction mixture. These improved reaction conditions were very gratifying: we had optimized the reaction from requiring 10 mol % of Pd to just 1 mol %, moved from organic to aqueous conditions, and increased the overall efficiency of the system (Table 1, entry 13 compared with entry 1).[20]

Having seemingly optimized the chemistry we were eager to apply it to a range of amidines to determine its generality. As part of this the unactivated amidine **3** was cyclized to give the benzimidazole **4** (Table 2, entry 1). However, it was found that 3 mol % of Pd was required. Given this result and that the amidine was now unactivated we attempted to further develop the conditions (Table 2).

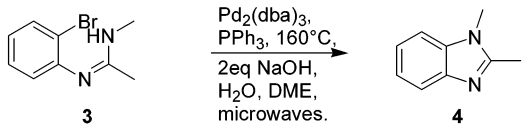
Having decreased the catalytic loading to 1 mol % of Pd, the concentration was increased with the view that this would enhance the reaction rate (Table 2, entries 2 and 3). Surprisingly, this had very little effect on the conversion. Even increasing the amount of catalyst (Table 2, entry 4) did not have a significant effect. We thought that the proportion of water to DME might be critical in limiting the reaction rate. Therefore, we were pleased to find that complete conversion could be achieved by changing the solvent ratio to 50% water (Table 2, entry 5). To determine if this was the most favorable ratio further experiments were carried out (Table 2, entries 6−8). Clearly, as the proportion of water was increased

(18) A laboratory microwave instrument with a monomodal cavity and sealed reaction vessels was used: a Smith Creator available from Personal Chemistry AB, Uppsala, Sweden.

(19) This is in contrast to observations by Hartwig, see: Hartwig, J. F. *Synlett* **1997**, 329−340.

(20) A control reaction in the absence of any palladium catalyst was carried out. After 167 min at 160 °C a 28% conversion was achieved.

TABLE 2. Continued Optimization of the Aryl-Amination Reaction

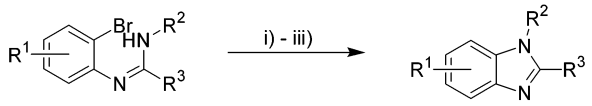


3 4

entry	mol % of Pd[a]	% of water[b]	concn of amidine/M	time/ min	conversion[c]/ %
1	3	25	0.065	17	>98
2	1	25	0.26	50	36
3	1	25	0.52	33	41
4	2	25	0.52	33	48
5	2	50	0.52	17	>98
6	1	50	0.52	33	49
7	1	67	0.52	17	37
8	1	90	0.52	17	18

[a] A 4-fold amount of PPh_3 was used relative to Pd. [b] The percentage of water in a water/DME mixture. [c] Conversions were determined by ^1H NMR.

TABLE 3. Application of the Benzimidazole Synthesis to Electron Poor, Neutral, and Rich Amidines[a]



entry	R^1	R^2	R^3	mol %[b]	time/min	yield/%
1	5-NO_2	Me	Me	0.5	10	66
2	5-NO_2	Ph	Me	0.5	5	83
3	5-NO_2	i-Pr	Me	0.25	9	79
4	5-H	Me	Me	1	17	86
5	5-H	Ph	Me	0.5	17	91
6	5-H	Me	Ph	1	17	95
7	5-OMe	Me	Me	1.5	67	81
8	5-OMe	Ph	Me	1.5	17	92
9	3-Me	Me	Me	1	17	98
10	3-Me	Ph	Me	0.5	10	98

[a] Reagents and conditions: (i) $Pd_2(dba)_3$, PPh_3, 2 equiv of NaOH, 50% H_2O/DME, 160 °C, microwaves; (ii) Amberlyst 15, DCM; (iii) 50% Et_3N/DCM. [b] This refers to mol % of $Pd_2(dba)_3$; an 8-fold amount of PPh_3 was used.

the conversion fell, indicating that 50% water was the optimum amount.

Having thoroughly optimized the reaction conditions,[21] we turned our attention to the purification of the benzimidazoles. A quantitative conversion from the amidine to benzimidazole was occurring; however, due to the use of PPh_3 the resultant compounds were contaminated with phosphine residues. We thought it might be possible to employ a "catch and release" strategy, whereby the benzimidazole could be captured onto an acidic resin, and after washing, released back into solution in a pure form.[22] Thus, crude benzimidazole **4** was dissolved in DCM with Amberlyst 15 resin. After washing the resin to remove the phosphine contaminants, the benzimidazole was released from the Amberlyst with Et_3N and filtered. Removal of the solvents gave benzimidazole **4** in a high yield, with no trace of the original phosphine impurity.

At this point with improved conditions for the benzimidazole synthesis and having developed a purification method, we applied the methodology to a variety of amidines (Table 3).

The methodology was applied to electron poor (Table 3, entries 1−3), neutral (Table 3, entries 4−6), electron rich (Table 3, entries 7 and 8), and sterically hindered (Table 3, entries 9 and 10) amidines. These results demonstrate the usefulness and general applicability of this chemistry: all the benzimidazoles were synthesized rapidly and in excellent yields. The amination of electron poor amidines was the most facile, as seen by the fact that these reactions required the lowest catalytic loading and shortest reaction times, while the electron rich amidines were the least reactive. Interestingly, the reaction rate was increased with amidines containing substituents near the reacting centers (Table 3, entries 3, 9, and 10). Presumably, the increased steric hindrance destabilizes the six-membered palladacycle intermediate,[23] thus making the reductive elimination more facile.

In conclusion, we have demonstrated a rapid and high-yielding synthesis of benzimidazoles. This has been achieved by a thorough optimization of the reaction conditions, leading to lower catalytic loadings, shorter reaction times, and a simple nonchromatographic purification method.

Experimental Section

General Procedure for the Synthesis of Benzimidazoles. To a solution of amidine (0.26 mmol) in DME (90 μL) in a microwave vial was added PPh_3 (106 μL, 0.2 M in DME, 8 mol %), NaOH (0.25 mL, 2.08 M in water, 2.0 equiv), and $Pd_2(dba)_3$ (53 μL, 0.05 M in DME, 1 mol %). (The reactions were always carried out in a total volume of 0.5 mL of solvent.) The vial was sealed with a crimped cap and the reaction mixture was heated in the Personal Chemistry Smith Creator microwave instrument at 160 °C. The reaction mixture was then diluted with EtOAc (15 mL), washed with brine (10 mL), and extracted with EtOAc (2 × 10 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo. The residue was dissolved in DCM (5 mL) with washed Amberlyst 15 resin (250 mg) and stirred for 18 h. The resin was then washed with DCM (2 × 5 mL) and PhMe (2 × 5 mL) and treated with a solution of 50% Et_3N/DCM (5 mL) for 1 h. The resin was washed with DCM (5 mL), the washings were collected, and the solvent was removed in vacuo to give the pure benzimidazole.

Supporting Information Available: Spectroscopic data and ^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Under these conditions, a thermal comparison was made with use of amidine **1**. The reaction was carried out in a sealed microwave vial and was heated in an oil bath, preheated at 160 °C. The reaction mixture was heated for approximately the same time as the reaction carried out in the microwave (approximate due to longer heating and cooling periods). After this time a quantitative conversion to the benzimidazole had been achieved.

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