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An intramolecular palladium-catalysed aryl amination reaction to produce benzimidazoles

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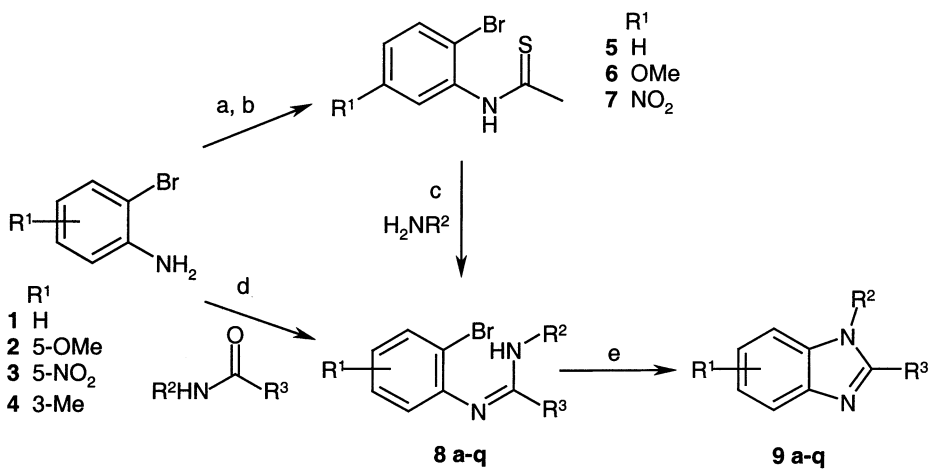
Abstract—A novel synthesis of benzimidazoles by a palladium-catalysed intramolecular *N*-arylation reaction from (*o*-bromophenyl)amidine precursors is described.

The benzimidazole nucleus is of significant importance to medicinal chemistry. Recent publications have reported benzimidazole-containing compounds showing biological activity as selective neuropeptide Y Y1 receptor antagonists,[1] 5-lipoxygenase inhibitors for use as novel antiallergic agents,[2] factor Xa (FXa) inhibitors,[3] poly(ADP-ribose)polymerase (PARP) inhibitors[4] and as human cytomegalovirus (HCMV) inhibitors.[5] The traditional synthesis of benzimidazoles involves the reaction between a phenylenediamine and a carboxylic acid or equivalent under harsh dehydrating reaction conditions.[6] More recent methods include a palladium-catalysed carbonylation reaction of a phenylenediamine followed by cyclodehydration,[7] an intramolecular vicarious nucleophilic substitution of hydrogen to give 2-amino-4-nitrobenzimidazoles[8] and a rhodium-catalysed hydroformylation of *N*-alkenyl phenylenediamines.[9] Benzimidazoles have also been prepared on solid-phase to provide a combinatorial approach.[10] A limitation with the majority of benzimidazole syntheses is that *N*-substitution is generally non-regioselective and a mixture of isomers is often obtained. Purification and characterisation of the two regioisomers can also be problematic.



Scheme 1. *Reagents and conditions*: (a) AcCl (1.1 equiv.), Et_3N (1.1 equiv.), CH_2Cl_2, rt, 1 h; (b) Lawesson's reagent (1 equiv.), THF, microwaves (Labwell MW10 instrument); 5×1 min (100 W), sealed tube; (c) $HgCl_2$ (1.5 equiv.), amine (5 equiv.), THF, rt 18 h; (d) amide (1.1 equiv.), $POCl_3$ (1.5 equiv.), Et_3N (1.1 equiv.), toluene, reflux, 18 h; (e) $Pd(PPh_3)_4$ (5–10 mol%), K_2CO_3 (1.6 equiv.), NaO^{t}Bu (1.6 equiv.), toluene, reflux, 18 h.

Keywords: benzimidazoles; palladium-catalysed *N*-arylation reaction.

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Table 1. Data for the synthesis of benzimidazoles **9**

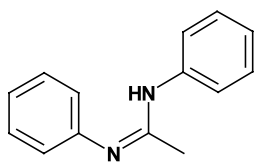
8, **9**	Yield of **8** (%)[a]	R^1	R^2	R^3	Yield of **9** (%)[a]
a	96[b]	H	Me	Me	87
b	50[b]	H	Et	Me	58
c	88[b]	H	^{i}Pr	Me	70
d	83[b]	H	Bn	Me	100[c]
e	90[b]	H	2-Methoxyethyl	Me	69
f	61[b]	H	Cyclopentyl	Me	70
g	75[b]	5-OMe[d]	Me	Me	68
h	78[b]	5-OMe[d]	Bn	Me	90
i	24[e]	H	Ph	Me	55
j	41[e]	5-OMe[d]	Ph	Me	45
k	96[e]	5-NO_2[d]	Me	Me	71
l	54[e]	5-NO_2[d]	^{i}Pr	Me	91[f]
m	54[e]	5-NO_2[d]	Ph	Me	86
n	47[e]	7-Me[d]	Ph	Me	99
o	63[e]	7-Me[d]	Me	Me	60
p	83[e]	H	Me	Ph	90
q	54[e]	H	Me	1-Pyrrolidinyl	90

[a] Yields refer to isolated products after purification which were characterised by ^{1}H, ^{13}C NMR and LC–MS.
[b] From the corresponding thioamide using $HgCl_2$ method.
[c] Isolated as a 3:1 mixture with Ph_3PO by ^{1}H NMR.
[d] Numbering is in relation to the benzimidazoles.
[e] From the corresponding aniline using $POCl_3$ method.
[f] Isolated as a 4:1 mixture with Ph_3PO by ^{1}H NMR.

Intramolecular palladium-catalysed *N*-arylation reactions of aryl halides have been used to prepare indoles,[11] pyridoindoles,[12,13] pyrido[1,2-*a*]benzimidazoles[13] and other heterocycles.[14] The reaction has also been applied to natural product synthesis.[15] This strategy would be particularly attractive for the synthesis of benzimidazoles, since it would provide a flexible route and allow for regioselective *N*-substitution. We now report a novel synthesis of benzimidazoles **9** by a palladium-catalysed *N*-arylation reaction from (*o*-bromophenyl)amidine precursors **8** (Scheme 1).

Synthesis of the (*o*-bromophenyl)amidines **8a**–**h** (Table 1) was achieved in three steps (Scheme 1). Acetylation of 2-bromoaniline **1** and 2-bromo-5-methoxyaniline **2**, followed by thionation with Lawesson's reagent under microwave conditions provided the thioamides **5** and **6**, respectively (81, 83% yields). Treatment of the thioamides with mercury(II) chloride and the corresponding amines produced the desired amidines **8a**–**h** in good yields.[16] Thioamides **5** and **6** failed to react with aniline, however, and only starting materials were isolated, even after prolonged heating. Synthesis of amidines **8k**–**m** was also attempted by this method: acetylation of 2-bromo-5-nitroaniline **3** gave the amide which was thionated to produce the thioamide **7** in 54% yield. Subsequent treatment of **7** with mercury(II) chloride and either methylamine, isopropylamine or aniline failed to produce any amidine products, with only starting material being isolated in each case. A more direct approach was then adopted for these amidines: 2-bromo-5-nitroaniline was heated with the corresponding amide and $POCl_3$ in toluene to produce the desired amidines **8k**–**m** in variable yields (54–96%). This route was also successful for the synthesis of amidines **8i**–**j**, **8n**–**o** and **8p**–**q**, starting from the corresponding anilines. It is worth noting that amidines **8j** and **8n** were isolated as a 2:1 mixture with a side-product, identified as **10** (Fig. 1), which was separable by preparative HPLC. No side-products were isolated from any of the other reactions. No attempt was made to optimise these reaction reactions.

The palladium-catalysed cyclisation was initially attempted on the simple amidine **8a** and Buchwald's conditions[14] for intramolecular *N*-arylation reactions were investigated. No reaction was observed using $Pd_2(dba)_3$ (3 mol%)/P(*o*-tolyl)$_3$ (5 mol%) with either Cs_2CO_3, K_2CO_3 or NaO^{t}Bu in *m*-xylene after 18 h under reflux. Only **8a** was recovered from the reaction mixtures. The same result was obtained when $Pd(OAc)_2$ (10 mol%) and Na_2CO_3 were heated under reflux with **8a** in DMF for 18 h. Reaction of **8a** with $Pd_2(dba)_3$ (5 mol%)/BINAP (5 mol%) in toluene for 18 h under reflux was successful with benzimidazole **9a** being produced in 88% yield after purification. Similarly, treatment of **8a** with (5–10 mol%) $Pd(PPh_3)_4$[17] and a mixture of NaO^{t}Bu (1.6 equiv.) and K_2CO_3 (1.6 equiv.)[†] in toluene for 18 h under reflux



10

Figure 1.

[†] Buchwald[14b] reported that although K_2CO_3 was not essential in intramolecular amination reactions, cleaner transformations were generally obtained when it was employed. The reactions described herein were as clean whether K_2CO_3 was used or not.

produced **9a** in 87% yield after purification. The latter procedure was adopted as a standard set of conditions and was applied to the cyclisations of the remaining amidines **8b**–**q** (Table 1). The reactions proceeded smoothly and were all complete after 18 h under reflux in toluene to give the benzimidazoles **9b**–**q**. Yields were generally good to excellent.‡

Some interesting observations can be made from these results. Most importantly, both electron withdrawing (**8k**–**m**) and electron donating (**8g**,**h**,**j**) groups *para* to the amidine bromo substituent were tolerated. Similarly, amidines **8n**–**o**, which contained a methyl group *ortho* to the bromo substituent, cyclised successfully. A range of substituents on the amidine nitrogen was tolerated and the guanidine **8q** also cyclised efficiently to give the 2(1-pyrrolidinyl) benzimidazole **9q**.

In summary, we have developed a palladium-catalysed *N*-arylation reaction which provides a novel synthesis of benzimidazoles from (*o*-bromophenyl)amidine precursors. The route is flexible and allows for the preparation of highly substituted benzimidazoles including regioselective *N*-substitution. Work is currently underway to optimise and extend the scope of this procedure.

‡ General procedure: To a solution of **8** (0.2 mmol) in toluene (5 ml) under argon was added K_2CO_3 (1.6 equiv.), NaO^{t}Bu (1.6 equiv.) and $Pd(PPh_3)_4$ (5–10 mol%) sequentially and the resulting mixture was heated under reflux for 18 h. The reaction mixture was filtered through Celite and the solvent was removed in vacuo. The crude residue was purified either by column chromatography or preparative HPLC to give **9**. Data for new compounds. **9e**: colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) 7.67–7.69 (1H, m, ArH), 7.29–7.30 (1H, m, ArH), 7.20–7.23 (2H, m, ArH), 4.27 (2H, t, *J* 5.5, CH_2), 3.68 (2H, t, *J* 5.5, CH_2), 3.26 (3H, s, OCH_3), 2.62 (3H, s, CH_3); ^{13}C NMR (100 MHz, DMSO) 152.3, 142.3, 135.2, 121.3, 121.1, 118.1, 110.0, 70.5, 58.4, 43.1, 13.7; *m*/*z* (ES$^+$) 191 (M$^+$+1, 100%); HRMS 191.1184 (measured), 191.1184 (calculated). **9f**: white solid; mp 102–103°C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.74 (1H, dd, *J* 6.7, 2.0, ArH), 7.42 (1H, dd, *J* 6.7, 2.0, ArH), 7.21–7.28 (2H, m, ArH), 4.76 (1H, quint, *J* 8.9, CH), 2.69 (3H, s, CH_3), 2.06–2.23 (6H, brm, 3×CH_2), 1.81–1.85 (2H, m, CH_2); ^{13}C NMR (100 MHz, DMSO) 151.8, 140.8, 132.4, 121.9, 121.7, 117.9, 111.6, 56.2, 29.6, 24.6, 14.0; *m*/*z* (ES$^+$) 201 (M$^+$+1, 100%); HRMS 201.1381 (measured), 201.1382 (calculated). **9n**: white solid; mp 115–118°C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.62 (1H, d, *J* 8.0, benzimidazole H-4), 7.55–7.56 (3H, m, ArH), 7.37–7.39 (2H, m, ArH), 7.16 (1H, m, benzimidazole H-5), 6.94 (1H, d, *J* 7.3 benzimidazole H-6), 2.38 (3H, s, CH_3), 1.92 (3H, s, CH_3); ^{13}C NMR (100 MHz, DMSO) 151.8, 142.6, 137.3, 134.5, 129.3, 128.9, 124.3, 121.6, 120.7, 116.5, 17.4, 14.0; *m*/*z* (ES$^+$) 223 (M$^+$+1, 100%); HRMS 223.1233 (measured), 223.1235 (calculated). **9q**: (isolated as a formate salt) white solid; mp 34–36°C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.46 (1H, s, formate-H), 7.54 (1H, dd, *J* 6.8, 1.4, ArH), 7.14–7.23 (3H, m, ArH), 3.74–3.80 (7H, m, CH_3+2×CH_2), 2.06–2.09 (4H, m, 2×CH_2); ^{13}C NMR (100 MHz, DMSO) 163.2, 156.4, 141.5, 136.1, 120.8, 119.1, 115.3, 108.1, 49.8, 30.9, 25.2; *m*/*z* (ES$^+$) 202 (M$^+$+1, 100%); HRMS 202.1342 (measured), 202.1344 (calculated).

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