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Synthesis of pyrimido[4,5-*b*]indoles and benzo[4,5]furo[2,3-*d*]pyrimidines via palladium-catalyzed intramolecular arylation

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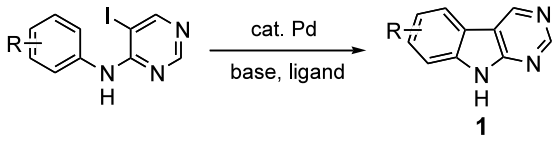
Abstract—Various pyrimido[4,5-*b*]indoles and benzo[4,5]furo[2,3-*d*]pyrimidines were synthesized via a palladium-catalyzed intramolecular arylation of pyrimidine substrates. Thus, 4-aryloxy- or 4-anilino-5-iodopyrimidines were treated with $Pd(OAc)_2(PPh_3)_2$ and base in DMF to give the regioselective cyclized heterocycles.

Heterocycles containing a pyrimidoindole moiety attract considerable interest in pharmaceutical research due to their wide range of biological activity. A number of pyrimido[4,5-*b*]indole derivatives have been reported to show significant anti-hypertensive activity, anti-inflammatory activities,[2] or act as A1 adenosine receptor antagonists,[3] CFR1 and neuropeptide Y receptor ligands[4] and potential tyrosine kinases (PTK) inhibitors.[5] The synthesis of pyrimidoindoles generally applies to one of the following approaches: (1) construction of the pyrimidine ring via the condensation of 2-amino-3-cyanoindole with formic acid or 2-amnio-3-indolecarboxylate with formamide or nitrile;[1,6] (2) intramolecular amination of 4-halo-5-arylpyrimidines;[7] and (3) the photochemical reaction of tetrazolo-pyrimidines.[8] The analogous heterocyclic benzo[4,5]-furo[2,3-*d*]pyrimidines are rare in themselves and a very limited amount of synthetic effort towards these that have been reported. These routes usually utilize intramolecular Diels–Alder reactions of *as*-triazine derivatives[9a] or are prepared from 2-amino-3-cyanobenzofurans.[9b]

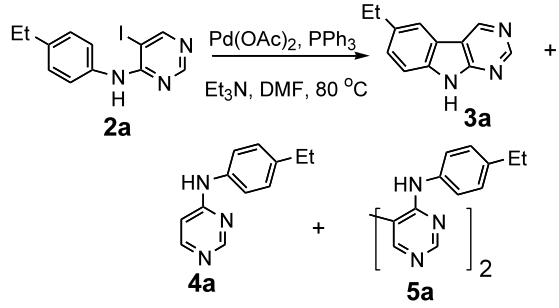
All of these reported methods for substituted-benzene derivatives either required long sequences or are operatively not practical for pharmaceutical research labs. Therefore, in order to develop a convenient synthetic method allowing a variety of substituents (R-) on the benzene ring (**1**, Scheme 1) we began to explore palladium chemistry on this system. It has been reported



Scheme 1.

that the Pd-mediated biaryl coupling reactions proceed at high temperature (120–150°C);[10] however, the Pd-catalyzed arylation on a pyrimidine system has not been explored. As a result, we have developed a general procedure for the intramolecular cyclization of 5-iodopyrimidines for the syntheses of pyrimido[4,5-*b*]-indole and benzo[4,5]furo[2,3-*d*]pyrimidine derivatives.

Our initial attempt to affect the Pd-catalyzed intramolecular arylation through addition of $Pd(OAc)_2$-$(PPh_3)_2$ (10 mol%), Et_3N (1.5 equiv.) to pyrimdine **2a** in DMF (0.5 M) at 80°C gave the cyclized product **3a** along with the deiodinated by-product **4a** and the homocoupled product **5a** in a ratio of 4.5:2:1 (Eq. (1)).



(1)

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Since tertiary amines have been found to act as hydride donors in palladium-catalyzed reactions,[11] we investigated the effect of bases on the internal arylation of 4-anilino-5-iodopyrimidine. Different solvents, palladium catalysts and ligands were also examined. The results are summarized in Table 1.

We found that the catalysts and ligands had a profound effect on the reaction yield. The catalyst $PdCl_2(PPh_3)_2$, which is mostly used in this type of arylation reaction, provided a 55% yield of product **3a**, whereas, $Pd(OAc)_2(PPh_3)_2$ provided **3a** in 86% yield. The bidentate ligand (±)-BINAP also proved to be effective in this case and gave 65% yield. The use of $Pd_2(dba)_3$/dppp (Table 1, entry 5) led to complex results, where 27% of **3a**, 5% of deiodinated **4a**, 2% of homocoupled by-product **5a** and 24% of starting material **2a** were observed. The reaction resulted in a 49% yield of **3a** when the bulkier ligand, 2(di-*t*-butylphosphino)biphenyl (Table 1, entry 4) was used. To our surprise, under the conditions ($Pd(OAc)_2$/NaOAc), which usually effected the internal arylations,[10] the reaction was extremely slow and gave only 13% of **3a** with 33% of starting material **2a** remaining after 48 h.

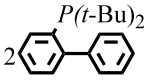
The effect of base on the reaction was also investigated. The reaction rate was increased by using the organic base Et_3N (Table 1, entry 7). The starting material was completely consumed in 7 h; however, by-products **4a** and **5a** were also formed along with the desired cyclized **3a**. The replacement of Et_3N with an inorganic base such as NaOAc circumvented the side reactions completely. No by-products were observed by HPLC analysis. Other bases that have been explored include Cs_2CO_3, $NaOBu^t$, and $NaHCO_3$. However, only Cs_2CO_3 provided a satisfactory yield (60%) though this was not as effective as NaOAc.

A study of the influence of different solvents (DMF, DMA, dioxane, CH_3CN) suggested that DMF (85°C) or DMA (100°C) were the best choices. No reaction was observed at 70°C or lower.

In order to determine the versatility of this intramolecular arylation process on a pyrimidine system, a number of pyrimido[4,5-*b*]indole derivatives were synthesized by employing the optimized reaction condition, $Pd(OAc)_2(PPh_3)_2$/NaOAc/DMF. The various 4-anilino-5-iodopyrimidines were prepared from 4-chloro-5-iodopyrimidine[12] and the appropriate anilines in refluxing EtOH in good yields (Table 2).

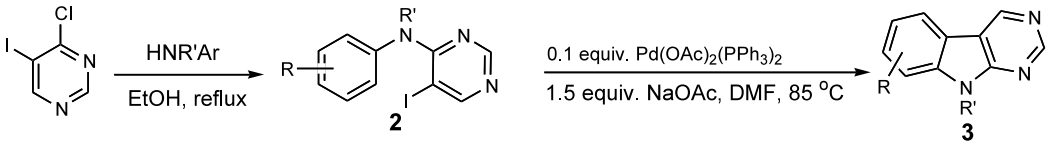
Compounds **2** bearing various substituents on the anilino portion, were then subjected to $Pd(OAc)_2$-$(PPh_3)_2$ (10 mol%), NaOAc (1.5 equiv.) in DMF (0.01 M) at 85°C, leading to the cyclized products **3** in moderate to good yields. The *N*,*N*-disubstituted anilinopyrimidine **2f** also underwent the cyclization in 51% yield. Generally, the reaction occurred at the less hindered site on the aromatic ring. For example, only a single product was isolated from the reactions of pyrimidines **2c**, **2g** and **2j**. The reaction of the substrate **2d** with trimethoxy groups on the phenyl ring also proceeded well to give a 64% yield of **3d**. Interestingly, the reaction of pyrimidine **2i** gave a mixture of two products, **3i** and **3i′** in a ratio of 1.8:1 (determined by crude ^1H NMR).

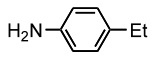
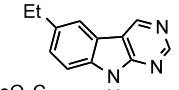
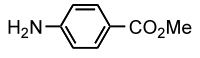
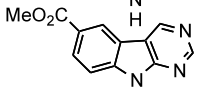
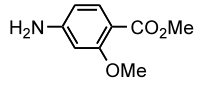
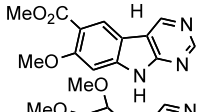
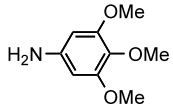
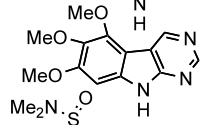
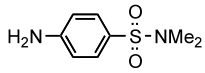
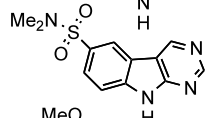
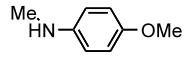
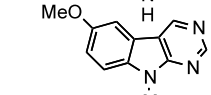
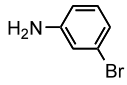
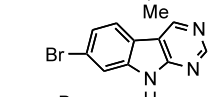
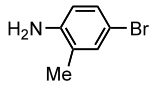
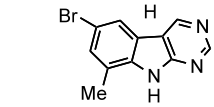
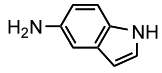
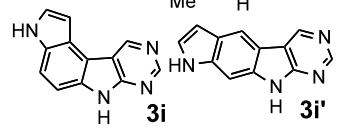
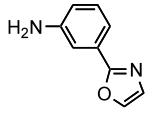
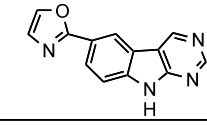
Table 1. Effect of Pd catalysts, ligands, bases and solvents on the intramolecular arylation of **2a**[a]

Entry	Pd catalyst	Ligand	Base	Solvent	Time (h)	Yield[b] (%)
1	$Pd(OAc)_2(PPh_3)_2$	–	NaOAc	DMF	36	86
2	$PdCl_2(PPh_3)_2$	–	NaOAc	DMF	48	55
3	$Pd(OAc)_2$	(±)-BINAP	NaOAc	DMF	48	65
4	$Pd(OAc)_2$		NaOAc	DMF	48	49
5[c]	$Pd_2(dba)_3$	2 dppp	NaOAc	DMF	72	27
6	$Pd(OAc)_2$	–	NaOAc	DMF	48	13
7[d]	$Pd(OAc)_2(PPh_3)_2$	–	Et_3N	DMF	7	42
8	$Pd(OAc)_2(PPh_3)_2$	–	Cs_2CO_3	DMF	36	60
9	$Pd(OAc)_2(PPh_3)_2$	–	$NaHCO_3$	DMF	48	39
10[e]	$Pd(OAc)_2(PPh_3)_2$	–	$NaOBu^t$	DMF	48	2
11[f]	$Pd(OAc)_2(PPh_3)_2$	–	NaOAc	DMA	30	88
12	$Pd(OAc)_2(PPh_3)_2$	–	NaOAc	Dioxane	36	71
13[g]	$Pd(OAc)_2(PPh_3)_2$	–	NaOAc	CH_3CN	48	8

[a] *Reaction conditions*: 10 mol% of catalyst/ligand, 1.5 equiv. of base in solvent (0.01 M) at 85°C.
[b] HPLC yield. All reactions were monitored by HPLC.
[c] A 5% of **4a** and 2% of **5a** were formed with a 24% of SM recovered.
[d] A 13% of **4a** and 7% of **5a** were formed; 0.5 M reaction solution.
[e] 30% of SM remained.
[f] The reaction was run at 100°C.
[g] The reaction was run at 80°C, 15% of SM recovered.

Table 2. Pd-catalyzed intramolecular arylation of 4-anilino-5-iodopyrimidines **2a**[a]



entry	HNR'Ar	2	yield (%)	3	yield[a] (%)
1		**2a**	84		74
2		**2b**	86		58
3		**2c**	81		53
4		**2d**	84		64
5		**2e**	89		60
6		**2f**	78		51
7		**2g**	84		36
8		**2h**	80		40
9		**2i**	75		46(3i) 26(3i')
10		**2j**	79		60

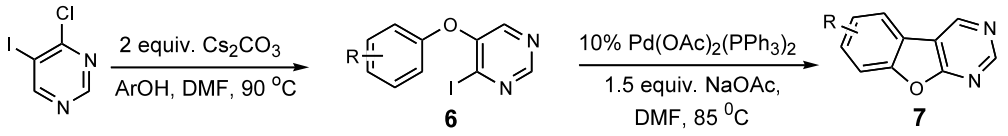
a All reactions were monitored by TLC. Isolated yield.

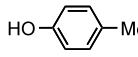
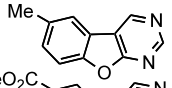
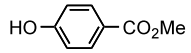
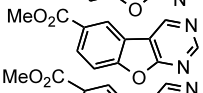
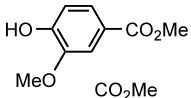
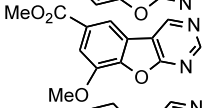
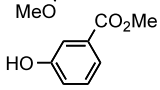
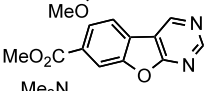
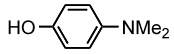
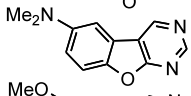
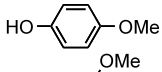
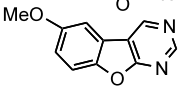
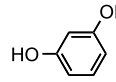
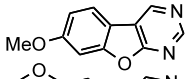
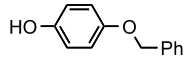
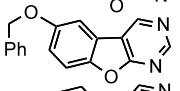
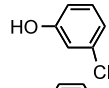
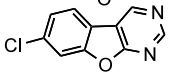
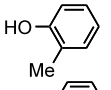
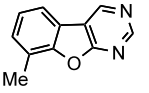
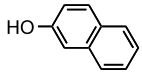
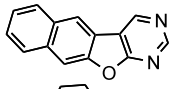
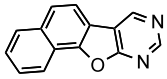
In an analogous manner, the intramolecular cyclization of 4-aryloxypyrimidine in the presence of $Pd(OAc)_2$-$(PPh_3)_2$ and NaOAc, led to the formation of benzo[4,5]-furo[2,3-*d*]pyrimidine derivatives. As shown in Table 3, treatment of 4-chloro-5-iodopyrimidine with various phenols and Cs_2CO_3 in DMF at 90°C gave the corresponding aryloxy-5-iodopyrimidines **6**. The optimized reaction condition for 4-anilino-5-iodopyrimidines also effected the cyclization of **6** to give the pyrimidobenzofurans **7**. The arylation reaction of **6**, typically completed in 7–12 h, was faster than that of the anilinopyrimidines **2**, which were completed in 24–48 h. Again, the cyclization was regioselective for the substrates **6d**, **6g**, and **6i**, in which cases, only a single product was isolated. The reaction of naphthyl substrate **6k** and **6l** (Table 3, entries 11 and 12) also proceeded well to give 54 and 65% yield of product, respectively.

Although the above method appears general, we have discovered some limitations to it. Substrates bearing strong electron-withdrawing groups on the phenoxy ring such as a nitro group did not undergo the intramolecular arylation. In addition, the six-membered ring formation from 4-benzyloxy-5-iodopyrimidine was also attempted with no desired product being formed.

Overall, a concise method for the synthesis of various pyrimido[4,5-*b*]indole and pyrimido[4,5-*b*]benzofuran derivatives was achieved by a two-step sequence. Nucleophilic displacement of 4-chloropyrimidines with anilines or phenols, followed by the intramolecular arylation reaction of 4-anilino- *or* 4-aryloxy-5-iodoyrimidines, provided the pyrimido[4,5-*b*]indole and pyrimido[4,5-*b*]benzofuran derivatives. This method provides a new entry into interesting heterocycles containing a pyrimidine ring.

Table 3. Pd-catalyzed intramolecular arylation of 4-aryloxy-5-iodopyrimidines



entry	ArOH	6	yield (%)	7	yield[a] (%)
1		**6a**	78		37[a] (60)[b]
2		**6b**	75		60
3		**6c**	73		58
4		**6d**	69		57
5		**6e**	40		50
6		**6f**	80		68
7		**6g**	60		64
8		**6h**	67		39
9		**6i**	74		36
10		**6j**	58		59
11		**6k**	54		54
12		**6l**	49		65

a Isolated yields. b HPLC yields

Supplementary material

Experimental details for the synthesis of compounds **2**, **3**, **6**, and **7** is provided. ^{1}H and $^{13}CNMR$ spectra and electronspray MS spectra are also included.

Acknowledgements

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