Two-Step Synthesis of 3-Aryl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-ones

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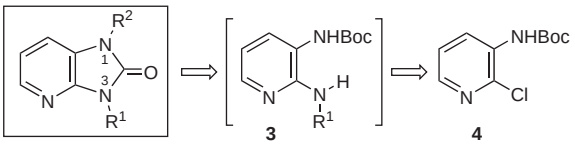
Abstract: One-pot tandem palladium-catalysed amination and intramolecular amidation of *tert*-butyl (2-chloropyridin-3-yl)carbamate with substituted primary anilines allows for the preparation of 3-arylated 1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-ones (49–90% yield) in two steps from commercially available materials.

Key words: palladium, amination, tandem reaction, ring closure



1: R^1, R^2 = H
2: R^1, R^2 = alkyl, aryl

Scheme 1

The 1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one ring system (**1**) constitutes the heterocyclic core of compounds possessing a diverse range of biological properties (Scheme 1). Indeed members of this structural class have demonstrated anti-inflammatory, analgesic and antidepressant activities amongst others.[1] General approaches which will allow facile exploration of structure–activity relationships within this class are therefore of value. The preparation of unsymmetrical 1,3-disubstituted imidazo[4,5-*b*]pyridin-2-ones **2** ($R^1 \neq R^2$) from 2,3-diaminopyridine as precursor is challenging and has required the use of protecting group strategies.[2] Access to **2** has also been described from 2-chloro-3-nitropyridine;[1b,1c] however, the sequence suffers from limited scope with low overall yields for the multistep sequence. A elegant approach based on the chemo- and regioselective palladium-catalysed amination of 3-iodo-2-chloropyridine has recently been reported[3] and permits the preparation of **2** (R^1 = aryl, R^2 = alkyl or aryl) in four steps from commercially available materials. In this letter, we report an alternative general approach to 3-arylated imidazopyridinones **2** (R^1 = substituted aryl and heteroaryl; R^2 = H) based on a tandem reaction sequence, which uses commercially available 3-amino-2-chloropyridine as the ultimate building block.

Our synthetic route is outlined in Scheme 1 and required amination of *tert*-butyl (2-chloropyridin-3-yl)carbamate (**4**) with a primary aniline (R^1NH_2) to afford an intermediate 2,3-diaminopyridine **3** (R^1 = substituted aryl and heteroaryl). We speculated that the 2-anilino nitrogen of **3** could engage in an intramolecular amidative ring closure to afford the desired cyclic ureas **2** (R^1 = aryl/heteroaryl; R^2 = H) in one-pot. To our surprise, no examples of transition-metal-catalysed amination of an aryl halide bearing a carbamate protected amine in the *ortho*-position have been previously reported.[4] A palladium-catalysed process would, however, be expected to allow the desired amination to take place in preference to competing amidation with the secondary carbamate moiety.[5] The protected aminochloropyridine **4**[6] is readily prepared on multigram scale from 2-chloro-3-aminopyridine using the conditions reported by Kelly for related aminopyridines (NaHMDS, Boc_2O, THF, 81% yield) and can be isolated by crystallisation from *i*-PrOH–water.[7,8]

An initial survey of bidentate phosphine ligands[9] for the Pd-catalysed amination of **4** with aniline quickly identified XantPhos[10,11] as most promising and established the viability of the proposed tandem process. The results of further optimisation of base, Pd precatalyst and solvent combination to maximise the conversion of chloropyridine **4**, by way of intermediate **3a**, to imidazopyridine **2a** are summarised in Table 1. The ethereal solvents tetrahydrofuran and dioxane were found to facilitate the intramolecular amidative conversion of **3a** to **2a** (entries 1–3, 4–6) in comparison to toluene when using Cs_2CO_3 as base with up to 86A% of **2a** formed in a mixture of toluene and tetrahydrofuran (entry 3). The addition of catalytic triethylamine[12] was not found to be beneficial (entry 7) whilst water suppressed ring closure of **3a** (entries 8–10). Further screening (entries 11–18) identified the combination of $Pd_2(dba)_3$ (3 mol%), XantPhos (6 mol%) with *t*-BuONa as base in refluxing tetrahydrofuran[13] (15 mL/g) as optimum. Under these conditions, **2a** was formed in up to 93A% (entry 16) and was isolated in 82% yield following chromatography.[14] Alternatively, a solvent combination of toluene–isopropanol (4:1) was also effective (entry 19).

Control experiments in which either $Pd_2(dba)_3$, XantPhos or *t*-BuONa were absent led to no consumption of **4** establishing that all three components are required (Table 1, entries 20–22). Thus, under these conditions, the process is Pd-catalysed and does not proceed by way of a simple S_NAr displacement of the 2-chloropyridine **4** by the aniline nucleophile. Further support for a mechanistic rationale proceeding by way of **3a** is provided by the observation that although urea **5** (readily formed by condensation of 3-amino-2-chloropyridine with phenyl-

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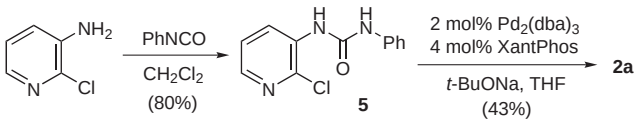
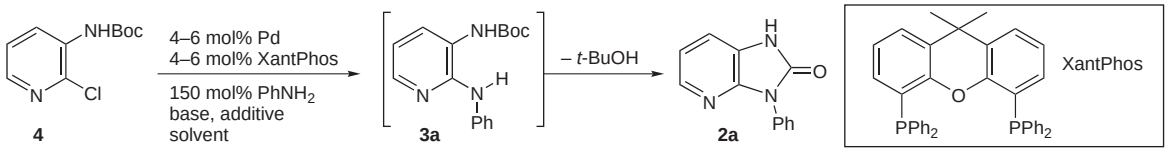


Scheme 2

isocyanate) does undergo intramolecular cyclisation to **2a** under the optimised conditions (Scheme 2), **5** is not observed in the conversion of **4** to **2a**.[15]

With conditions established for the one-pot conversion of **4** to **2a**, the scope of the aniline nucleophile in this process was evaluated (Table 2). A wide range of substituted anilines were found to be viable coupling partners affording the desired 3-arylated dihydroimidazopyridinones **2b**–**m** in moderate to excellent isolated yields. Electron-donating and electron-withdrawing substituents engendering ester, nitrile, alkoxy, fluoro, trifluoromethyl and chloro were tolerated on the aniline aromatic ring under the reaction conditions developed (entries 2–11).

Table 1 Optimisation of Reaction Conditions[a]

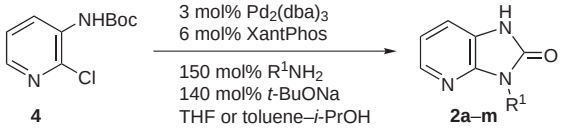


Entry[b]	Pd precatalyst (mol%)	Solvent (mL/g)	Base (mol%), additive (mol%)	HPLC of **2a** (A%)	HPLC of **3a** (A%)	HPLC of **4** (A%)
1	$Pd(OAc)_2$ (4)	toluene (10)	Cs_2CO_3 (130)	64	17	19
2	$Pd(OAc)_2$ (4)	dioxane (10)	Cs_2CO_3 (130)	73	0	26
3	$Pd(OAc)_2$ (4)	toluene (10), THF (1)	Cs_2CO_3 (130)	86	8	6
4	$Pd_2(dba)_3$ (2)	toluene (10)	Cs_2CO_3 (130)	78	18	2
5	$Pd_2(dba)_3$ (2)	dioxane (10)	Cs_2CO_3 (130)	76	0	24
6	$Pd_2(dba)_3$ (2)	toluene (10), THF (1)	Cs_2CO_3 (130)	65	0	35
7	$Pd_2(dba)_3$ (2)	toluene (10)	Cs_2CO_3 (130), Et_3N (10)	65	21	13
8	$Pd_2(dba)_3$ (2)	toluene (10)	Cs_2CO_3 (130), H_2O (130)	4	42	54
9	$Pd_2(dba)_3$ (2)	toluene (10)	Cs_2CO_3 (130), H_2O (250)	40	49	11
10	$Pd_2(dba)_3$ (2)	toluene (10)	Na_2CO_3 (140), H_2O (140)	3	75	22
11	$Pd_2(dba)_3$ (2)	toluene (15), THF (5)	*t*-BuONa (130)	83	0	17
12	$Pd_2(dba)_3$ (2)	toluene (15), THF (5)	*t*-BuONa (250)	84	0	16
13	$Pd_2(dba)_3$ (3)	toluene (15)	*t*-BuONa (140)	67	15	18
14	$Pd_2(dba)_3$ (3)	toluene (20)	*t*-BuONa (140)	63	19	18
15	$Pd_2(dba)_3$ (3)	toluene (15)	*t*-BuONa (140)	87	6	7
16	**$Pd_2(dba)_3$ (3)**	**THF (15)**	***t*-BuONa (140)**	**93 (82)**[c]	**5**	**2**
17	$Pd_2(dba)_3$ (3)	THF (15)	*t*-BuOK (140)	80	20	2
18	$Pd_2(dba)_3$ (3)	toluene (20)	*t*-BuOK (140)	83	11	6
19	**$Pd_2(dba)_3$ (3)**	**toluene–*i*-PrOH (20)**[d]	***t*-BuONa (140)**	**87**	**2**	**9**
20	$Pd_2(dba)_3$ (3)	THF (15)	None	0	0	100
21	None	THF (15)	*t*-BuONa (140)	0	0	100
22	$Pd_2(dba)_3$ (3)	THF (15)	*t*-BuONa (140)(no XantPhos)	0	0	100

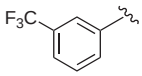
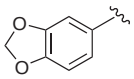
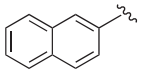
[a] Reactions were performed at reflux for 18–23 h under N_2 with 150 mol% $PhNH_2$. HPLC A% were determined by reverse-phase analysis on a Betasil C18 4.6 × 250 mm, 3 μm column at 210 nm.
[b] Entries 1–12, XantPhos (4 mol%); entries 13–21, XantPhos (6 mol%); entry 22, no XantPhos added.
[c] Isolated yield following purification by chromatography.
[d] Toluene–*i*-PrOH (4:1).

ortho-Substituents were viable (entries 4, 11) although in the case of 2-methylaniline, a significant level of intermediate **3k** (R^1 = 2-MeC_6H_4) remained after 24 hours, presumably due to steric encumbrance in the cyclisation to form **2k**. Use of heterocyclic amines was also possible with the coupling of 3-aminopyridine (entry 12) proceeding uneventfully. However, 2-aminopyrazine was unreactive (entry 13). Due to the high polarity and consequent low solubility of the product pyridinones, the solvent combination of toluene–isopropanol (4:1) was superior to THF in some instances, resulting in less viscous reaction mixtures. In general, the product imidazopyridinones were isolated by filtration through a silica plug followed by recrystallisation.[14,16] The further functionalisation of the 1-position nitrogen of imidazopyridin-2-ones of type **2a–l** by alkylation has been previously reported[1a] and thereby provides potential access to diverse unsymmetrically 1,3-disubstituted imidazo[4,5-*b*]pyridin-2-ones **2**.

Table 2 Scope of Aniline Nucleophile (R^1NH_2)



4 **2a–m**

Entry	Product	R^1 substituent	Yield (%)[a]
1	**2a**	Ph	82[b]
2	**2b**		86[b]
3	**2c**		90[b]
4	**2d**	2-$MeOC_6H_4$	78[c]
5	**2e**	3-$MeOC_6H_4$	67[c]
6	**2f**	2,4-$F_2C_6H_3$	77[b]
7	**2g**	4-*t*-$BuO_2CC_6H_4$	70[c]
8	**2h**	3-CNC_6H_4	52[c]
9	**2i**	3-ClC_6H_4	85[c]
10	**2j**		83[b]
11	**2k**	2-MeC_6H_4	49[b]
12	**2l**		86[b]
13	**2m**	2-Aminopyrazine	0[b]

[a] Yield after chromatographic purification and/or crystallisation.
[b] THF (15 mL/g) was used as solvent at reflux for 18–24 h.
[c] Toluene–*i*-PrOH (4:1, 20 mL/g) was used as solvent at 85 °C for 18–24 h.

To date, efforts to extend the scope of this tandem reaction sequence to encompass primary alkylamines have met with limited success. Under the conditions optimised for aniline coupling partners, only low levels of amination to form the desired 3-alkylated dihydroimidazopyridinones have been observed with unconverted chloropyridine **4** predominating in most instances along with other unidentified impurities.[17] Indeed the amination reactions of primary alkyl amines with heteroaryl chlorides, such as 2-chloropyridine, have typically had limited scope and required high catalyst loadings.[18,19] Further evaluation of alternative catalyst systems to address this limitation is currently pursued.[15]

In summary, we have developed a new synthetic entry to diversely substituted 3-arylated 1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-ones **2** (R^1 = aryl, heteroaryl; R^2 = H) in only two steps from commercially available 3-amino-2-chloropyridine. The tandem reaction sequence developed is palladium-catalysed and demonstrates a broad range of functional group tolerance with products isolated in moderate to excellent yields. As such, this synthetic approach should prove of utility in further evaluation of the structure–activity relationships of these biologically interesting compounds.

References and Notes

(1) (a) Clark, R. L.; Pessolano, A. A.; Shen, T.-Y.; Jacobus, D. P.; Jones, H.; Lotti, V. J.; Flataker, L. M. *J. Med. Chem.* **1978**, *21*, 965. (b) Robinson, M. M.; Finch, N. US Patent 3719683, **1973**. (c) von Bebenberg, W. US Patent 3819640, **1974**. (d) Lesher, G. Y.; Brundage, R. P.; Opalka, C. J.; Page, D. F. FP 2478637, **1981**; *Chem. Abstr.* **1982**, *96*, 85551k. (e) Kuezynski, L.; Mrozikiewiez, A.; Poreba, K. *Pol. J. Pharmacol. Pharm.* **1982**, *34*, 229. (f) Bianchi, M.; Butti, A.; Rossi, S.; Barzaghi, F.; Marcaria, V. *Eur. J. Med. Chem.* **1983**, *18*, 501. (g) Vaughn, J. R. Jr. US Patent 2637731, **1953**. (h) Rochling, H. F. W.; Buchel, K.-H.; Korte, F. W. A. G. K. US Patent 3459759, **1969**.

(2) Meanwell, N. A.; Sit, S. Y.; Gao, J.; Wong, H. S.; Gao, Q.; St. Laurent, D. R.; Balasubramanian, N. *J. Org. Chem.* **1995**, *60*, 1565.

(3) Kuethe, J. T.; Wong, A.; Davies, I. W. *J. Org. Chem.* **2004**, *69*, 7752.

(4) An aryl bromide example with an *ortho*-ethylcarbamate, presumably by way of an S_NAr mechanism, has been reported: Blanksma, J. J.; Verberg, G. *Recl. Trav. Chim. Pays-Bas* **1934**, *53*, 988.

(5) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.

(6) (a) Horino, H.; Ishiyama, T.; Tatematsu, T.; Makino, C.; Ochiai, Y.; Kito, K.; Kanaya, N.; Hishida, K. *Chem. Abstr.* **2001**, *135*, 166835. (b) Li, J.; Zheng, L.-M.; King, I.; Doyle, T.; Chen, S.-H. *Curr. Med. Chem.* **2001**, *8*, 121. (c) Niu, C.; Li, J.; Doyle, T. W.; Chen, S.-H. *Tetrahedron* **1998**, *54*, 6311.

(7) Kelly, T. A.; McNeil, D. W. *Tetrahedron Lett.* **1994**, *35*, 9003.

(8) **Preparation of *tert*-Butyl (2-Chloropyridin-3-yl)carbamate (4).**
To a stirred solution of NaHMDS (1 M in THF, 700 mL, 700 mmol) at –10 °C under N_2 was added a solution of 2-chloro-3-aminopyridine (40.9 g, 318 mmol) in THF (80 mL) over

10 min. The mixture was aged 10 min and then Boc_2O (72.9 g, 334 mmol) as a solution in THF (56 mL) was added over 10 min maintaining the internal temperature <8 °C. After aging 0.5 h, 2 M HCl (600 mL) and isopropyl acetate (400 mL) were added. The organic layer was washed with H_2O (200 mL) and concentrated in vacuo. The residue was crystallised from *i*-PrOH (250 mL) and H_2O (300 mL) to afford 58.9 g (81%) of **4** as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (1 H, d, *J* = 8.0 Hz), 8.02 (1 H, d, *J* = 4.4 Hz), 7.21 (1 H, dd, *J* = 8.4, 4.8 Hz), 7.01 (1 H, br s), 1.53 (9 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.1, 142.5, 139.1, 132.6, 127.0, 123.2, 81.8, 28.2. Mp 84–85 °C. MS (ES): *m*/*z* = 229 $[M + H]^+$.

(9) BINAP and dppf were found to be inferior for the formation of **2a** than XantPhos.

(10) First reported by van Leeuwen: Kranenberg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3081.

(11) XantPhos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

(12) The addition of Et_3N has been shown to provide rate enhancement in Pd-catalysed aryl iodide aminations when Cs_2CO_3 is employed as base. See: Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560.

(13) The THF used in our study had a water content between 60 mg/mL and 110 mg/mL as determined by Karl–Fischer titration.

(14) **Representative Procedure for the Preparation of 3-Phenyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (2a).**
A mixture of XantPhos (61 mg, 0.11 mmol, 6 mol%), $Pd_2(dba)_3$ (48 mg, 0.05 mmol, 3 mol%, 6 mol% Pd), *tert*-butyl (2-chloropyridin-3-yl)carbamate (**4**, 0.40 g, 1.75 mmol), aniline (0.24 g, 2.63 mmol, 150 mol%) and *t*-BuONa (0.24 g, 2.45 mmol, 140 mol%) in THF (6.0 mL, 15 mL/g) was degassed with N_2 and then heated at reflux for 18 h. After cooling to ambient, the reaction mixture was diluted with CH_2Cl_2 and filtered through a silica plug. Evaporation in vacuo and flash chromatography (EtOAc–heptane) afforded **2a** as a white solid (0.30 g, 82%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.40 (1 H, s), 7.94 (1 H, d, *J* = 4.8 Hz), 7.72–7.63 (2 H, m), 7.57–7.49 (2 H, m), 7.43–7.36 (2 H, m), 7.11–7.05 (1 H, m). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.1, 144.3, 140.2, 134.0, 129.2, 127.6, 126.6, 123.3, 118.5, 115.8. Mp 240–241 °C; Lit.[1a] 240–241 °C. MS (ES): *m*/*z* = 212 $[M + H]^+$.

(15) The approach used in Scheme 2 for the construction of 3-phenyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one has not been previously reported and given the diversity of commercially available isocyanates, may constitute another general entry to compounds in this class.

(16) All new compounds gave satisfactory spectroscopic characterisation data.

(17) Alkylamines screened were cyclopropylamine, *sec*-butylamine, (*R*)-1-phenylethylamine and 1-(2-aminoethyl)-piperidine. In all instances <20A% of desired imidazopyridin-2-one was identified by LCMS using either THF or toluene–*i*-PrOH (4:1) as reaction solvent.

(18) Use of a Josiphos ligand for amination of 2-chloropyridine with primary alkylamines has been recently reported: Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2005**, *44*, 1371.

(19) No examples of the preparation of 3-alkyl-substituted 1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-ones are documented in ref. 3 which employs $Pd_2(dba)_3$/BINAP as catalyst system for amination.