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Divergent synthesis of arylated pyridin-2(1*H*)-one derivatives via metal-catalysed cross-coupling processes

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ABSTRACT

1,5-Di(hetero)arylated-pyridin-2(1*H*)-one derivatives have been readily obtained in good yields starting from 2-fluoro-5-pyridylboronic acid. The sequence comprises three steps: (i) palladium-catalysed Suzuki-Miyaura reaction; (ii) base-catalysed hydrolysis; (iii) copper-catalysed C–N coupling. X-ray crystal structures are reported for selected pyridin-2(1*H*)-one derivatives. These compounds are of interest as new scaffolds for drug discovery.

1. Introduction

Functionalised pyridones are of continued interest due to their prevalence in naturally occurring compounds,[1–3] bioactive compounds and drugs,[4–14] coordination chemistry[15] and their catalytic acitivity.[16] New routes for their synthesis and functionalisation continue to be developed.[17,18] Metal-catalysed cross-coupling reactions have revolutionised the modification of pyridones[19] and related heterocycles, with C–C, C–N, C–O bond forming processes now widely utilised.[20,21] Notably, Suzuki-Miyaura, Buchwald-Hartwig and Ullmann type reactions have become ubiquitous in the post-functionalisation of heterocycles. Access to *N*-arylpyridones was traditionally achieved using harsh Ullmann-Goldberg conditions[22] resulting in low yields and poor functional group tolerance. Ligand-accelerated and copper-catalysed approaches have led to much milder coupling conditions.[23–28] Other methods for *N*-arylating pyridones and related heterocycles include: copper-mediated coupling with arylboronic acids,[24,29,30] lead-mediated coupling to aryl halides[31,32] and HATU-mediated coupling of arylamides to 4-hydroxyquinazolines.[33] There is interest in sequential metal-catalysed routes to functionalised heteroaryl systems.[34–39] The aim of the present work was to develop an efficient divergent route to tri-(hetero)aryl systems based on the pyridin-2(1*H*)-one framework starting from the commercially-available 2-fluoro-5-pyridylboronic acid **1**.[40] We also report related reactions of 2,6-difluoro-5-pyridylboronic acid.

2. Results and discussion

An overview of our methodology is shown in Scheme 1. Suzuki-Miyaura cross-coupling of 2-fluoro-5-pyridylboronic acid **1** with (hetero)aryl bromides **2**–**4** furnished compounds **5**–**7** under standard conditions[41,42] in high isolated yields (Table 1).

Conversion of **5**–**7** into the 2-pyridone derivatives **8**–**10** was achieved in high yields by hydrolysis under basic conditions (Table 1).[43] Compounds **6** and **7** reacted faster than **5**, presumably due to the electron withdrawing effect of the quinolyl and pyridyl substituents, respectively.

It has previously been observed that the copper-catalysed coupling of 2-pyridones can lead to both C–N and C–O arylated products.[28,44] To explore this reaction, pyridone derivative **8** was reacted with **11** (Scheme 2). After isolation of the *N*-heteroarylated product **12a** vide infra, a comparison with the crude ^{1}H NMR

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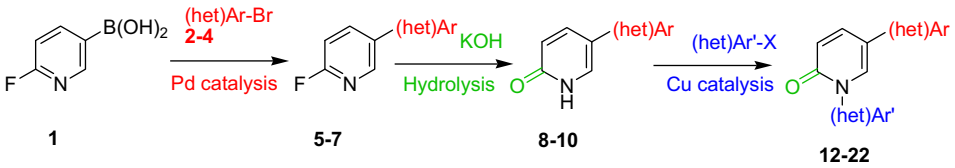
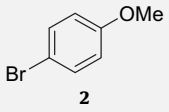
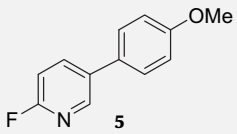
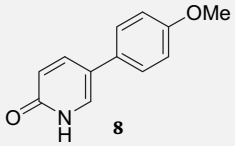
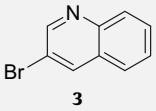
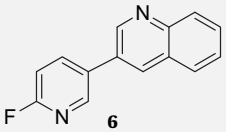
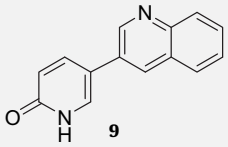
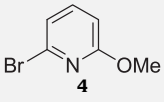
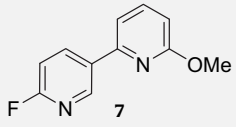
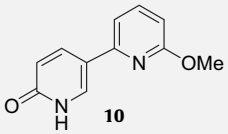
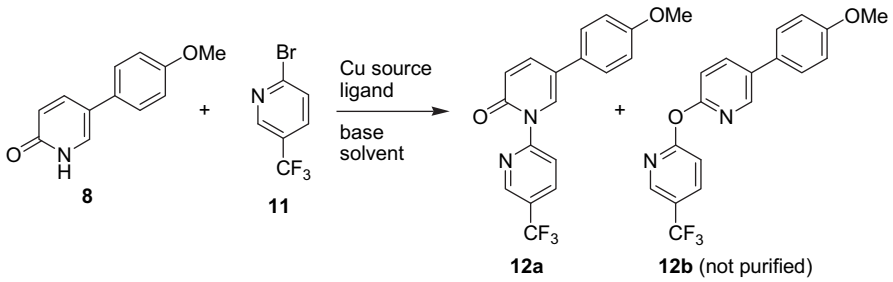


Scheme 1. Protocol for the three-step synthesis of 1,5-di(hetero)arylpyridin-2(1*H*)-one derivatives.

Table 1
Synthesis of fluoropyridines **5**–**7** and pyridones **8**–**10**

Entry	(het)Ar–Br	Cross-coupling product[c]	Yield[a] (%)	Hydrolysis product[d]	Yield[b] (%)
1	 **2**	 **5**	98	 **8**	83
2	 **3**	 **6**	89	 **9**	88
3	 **4**	 **7**	97	 **10**	92

[a] The quoted yields are for isolated product after purification by chromatography and/or recrystallisation.
[b] The quoted yields are for isolated product after acidification and filtration.
[c] Reagents and conditions: **1** (1.2–1.5 equiv), (hetero)arylbromide (1.0 equiv), $Pd(PPh_3)_2Cl_2$, Na_2CO_3 (3 equiv, 1 M in H_2O), 1,4-dioxane, reflux, 1–20 h under argon.
[d] Reagents and conditions: compound **5**, **6** or **7**, KOH (1 M in H_2O), 1,4-dioxane, reflux, 24–66 h.



Scheme 2. Coupling of **8** and **11**. For conditions see Table 2.

spectrum and GC–MS traces confirmed that **12a** was the major product. The other product, presumed to be **12b**, could not be obtained pure. An initial screening was undertaken utilising commonly employed conditions and ligands for the C–N coupling of 2-pyridones, 2-pyridazinones and NH-heterocycles (Table 2). Using 1,10-phenanthroline (1,10-phen) with conditions used previously for the N-heteroarylation of benzimidazole and other NH-heterocycles,[39] conversion was complete after 24 h with a 79:21 ratio of **12a**:**12b** (Table 2, entry 1). Buchwald's 4,7-dimethoxy-1,10-phenanthroline ligand has proved to be effective for the copper-catalysed N-arylation of 2-pyridone;[28] however, the high cost of the ligand led us to try cheaper alternatives. Whilst keeping the same base (Cs_2CO_3), the solvent was changed to dioxane, 8-hydroxyquinoline (8-HQ) was employed as the ligand and PEG was added as a solid–liquid transfer catalyst.[45] However, despite 8-HQ being previously used to *N*-arylated pyridones[44] and pyridazinones,[27] these conditions resulted in a low conversion and a reduced ratio

Table 2
Screening of conditions for arylation of **8** with **11**

Entry	Cu source	Ligand	Base	Solvent	GC–MS analysis **11**:**12a**:**12b**
1	CuI	1,10-phen	Cs_2CO_3	DMF	0:79:21
2	CuI	8-HQ	Cs_2CO_3	dioxane[a]	69:20:11
3	CuI	DMCDA	K_2CO_3	toluene	0:95:5
4	CuI	DMCDA	K_2CO_3	DMSO	3:97:0
5	Cu_2O	Chxn–Py–Al	Cs_2CO_3	MeCN	39:50:11

Conditions and reagents: **8** (0.735 mmol), **11** (0.700 mmol), Cu source (0.07 mmol), ligand (0.140 mmol), base (1.40 mmol), anhydrous solvent (2 mL), 100 °C, 36 h under argon.
[a] PEG (43 mg) additive used.