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An efficient copper-catalyzed coupling reaction of pyridin-2-ones with aryl and heterocyclic halides based on Buchwald's protocol

Chun Sing Li* and Darryl D. Dixon

Merck Frosst Centre for Therapeutic Research, Merck Frosst Canada & Co., PO Box 1005, Pointe-Clarie Dorval, Quebec, Canada H9R 4P8

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Abstract—An efficient copper-catalyzed coupling reaction based on the Buchwald's protocol has been established for pyridin-2-ones with aryl iodides, aryl bromides, and heterocyclic bromides.

Pyridin-2-one is an important component of many pharmacological active substances[1] and *N*-aryl substitution is frequently a key structural feature. Our ability to synthesize these *N*-aryl substituted pyridin-2-ones in a diverse and efficient manner would therefore offer the possibility to broaden the scope of SAR studies. N-arylation of amines under the copper-catalyzed Ullmann reaction usually requires drastic reaction conditions and produces moderate yields of the desired products.[2] However, improved conditions for the N-arylation of heterocyclic compounds have been reported.[3,4] Lam has also developed a copper-catalyzed cross-coupling reaction of N-heterocyclic compounds with aryl boronic acids to give *N*-aryl substituted heterocycles in fair to excellent yields.[5] Scope of this N-arylation has been studied with different substituted pyridin-2-ones.[6] Recently, Buchwald has developed an efficient copper-catalyzed system for the amination and amidation of aryl and heterocyclic halides.[7] This copper-catalyzed system provides an opportunity to easily access a number of *N*-aryl heterocyclic analogs, but the potential of this copper-catalyzed system in the synthesis of *N*-aryl substituted heterocyclic system has not yet been fully investigated. One recent example is the application to the synthesis of a *N*-aryl oxazolidinone,[8] which is a key structural feature of a new class of oxazolidinone antibiotics. Herein, we report our application of the Buchwald copper-catalyzed system to the cross-coupling reaction of pyridin-2-ones with aryl halides and discuss the scope and limitation of this synthetic reaction.

Buchwald's group has extensively investigated effects of ligands and bases on the copper-catalyzed coupling reaction.[9] We were pleased to see that *N*,*N*′-dimethylethylenediamine as the ligand and K_3PO_4 as the base could be conveniently used and gave very satisfactory results in our present study. Other ligands such as 1,2-diaminocyclohexanane were less effective although this ligand was successful in the oxazolidinone synthesis.[8] Replacement of K_3PO_4 with $CsCO_3$ gave poorer yield of the coupling product. The following conditions were used throughout this study: A screw cap 2-dram vial was charged with 1,4-dioxane (1.5 mL), pyridin-2-one (1 mmol), and aryl halide (1.2 mmol). CuI (40 mg, 0.2 mmol), *N*,*N*′-dimethyethylenediamine (44 L, 0.4 mmol), and K_3PO_4 (425 mg, 2 mmol) were added. The mixture was then flushed with nitrogen, capped and placed in an oil bath at 110 °C, and stirred for 16–24 h. After cooling to room temperature, the mixture was diluted with water and extracted with ethyl acetate. Purification over silica gel and elution with hexanes–ethyl acetate provided the desired coupling product.[10]

The coupling reaction of some representative pyridin-2-ones and aryl iodides were summarized in Table 1. Yields were in general very good. There were two exceptions. While a mild electron-withdrawing substituent on the pyridin-2-one such as a carboxylic ester in **1d** posed no problem in the coupling reaction, a strong electron-withdrawing substituent such as nitro

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* Corresponding author. Tel.: +1-514-428-3217; fax: +1-514-428-4900; e-mail: chunsing_li@merck.com

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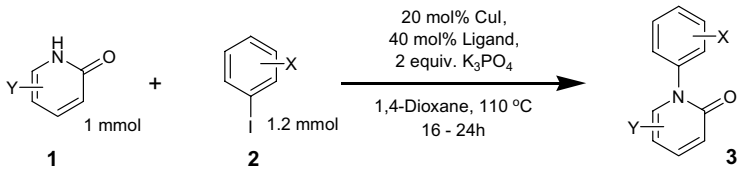
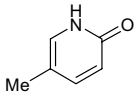
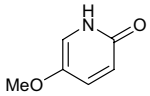
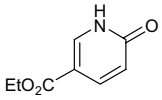
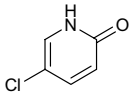
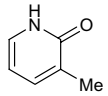
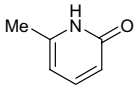
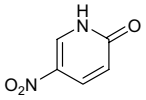
Table 1. Coupling reaction of pyridin-2-ones with aryl iodides



1 **2** **3**

	Pydridin-2-one **1**	(%) Yield of *N*-aryl pydirin-2-ones, **3** Aryl iodine **2**, X =					
		4-Me **2a**	3-OMe **2b**	4-OMe **2c**	4-CO_2ET **2d**	4-Cl **2e**	2-Me **2f**
1a		81	84	78	82	40	0
1b		94	78	91	92	85	
1c		87	82	90	81	75	
1d		77	92	69	95	55	
1e		68	90	67	83	50[a]	
1f		82	95	97	85	66	
1g				Trace	Trace		
1h				Trace	Trace		

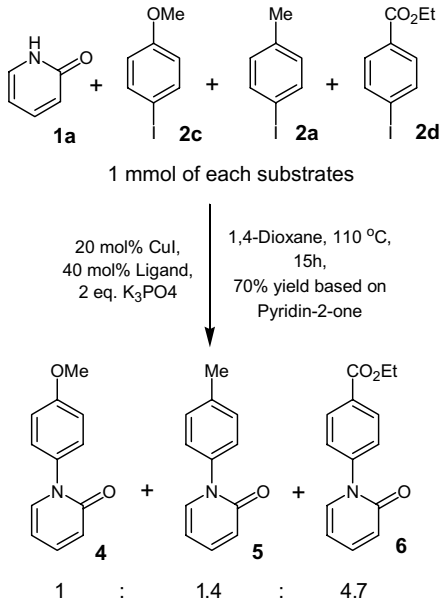
[a] 5% of dechlorinated product on the part of pyridin-2-one was also detected.

group in **1h**[11] impeded the coupling reaction. One of the reasons might be due to reduced nucleophilicity of the nitrogen atom on the pyridin-2-one. The coupling reaction also failed with substrates containing a substituent next to one of the reacting centers such as 2-iodo-toluene **2f** and 6-methyl-pyridin-2-one **1g**,[12] most likely due to steric effects. In general, a number of electron-withdrawing and donating substituents, either on the pyridin-2-one (**1c**[13] and **1d**) or the aryl iodide (**2b**, **2c**, and **2d**), were well tolerated. Although 4-chloro-1-iodo-benzene **2e** provided fair to good yield in the coupling reaction, the coupling reaction with 4-bromo-1-iodo-benzene was problematic. The bromine atom in the coupling product was found to be labile and would undergo a Finkelstein type reaction with iodide in the mixture.[14] The resulting iodide would then slowly lose the iodine to give the reduced product.

We were curious about effect of substituents on the rate of the coupling reaction and used a simple competition experiment to evaluate these effects on the aryl iodide (Scheme 1). An equimolar mixture of pyridin-2-one **1a**, aryl iodides **2c**, **2a**, and **2d** was reacted under the present conditions and gave pyridin-2-ones **4**, **5**, and **6** in a ratio of 1:1.4:4.7. This result demonstrated that an aryl iodide with an electon-withdrawing substitutent reacted more readily than a neutral substituent, which was in turn slightly more reactive than an aryl iodide with an electron-donating substituent.

Since aryl bromides are more readily commercially available, we then tested the coupling reaction with aryl bromides. This copper-catalyzed coupling reaction of pyridin-2-one was equally successful with aryl bromides (Table 2). Excellent yields of coupling products could also be obtained.

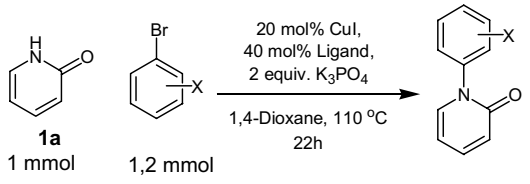
The use of bromide in the copper-catalyzed coupling reaction is particular suitable for heterocyclic substrates since the corresponding iodides are not always accessible. Some of the coupling reactions of pyridin-2-one **1a** with heterocyclic bromides were summarized in Table 3.



Scheme 1.

The coupling reaction gave excellent yields with 2-bromothiophene and 3-bromothiophene, but poorer yields with nitrogen-containing heterocycles such as 2-bromothiazole, 5-bromoindole, 8-bromoquinoline, and 3-bromopyridine.[15] Coordination of the nitrogen atom with the copper catalyst from these nitrogen-containing heterocycles might impede the catalytic process.

Table 2. Coupling reaction with aryl bromides

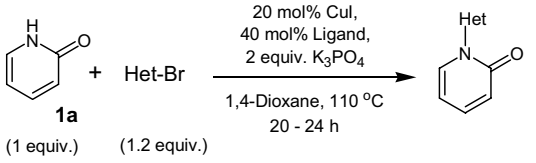


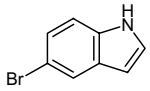
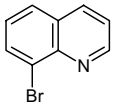
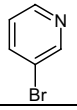
X	4-Me	4-OMe	4-CO_2Et
% Yield of *N*-aryl pyridin-2-ones	88	82	91

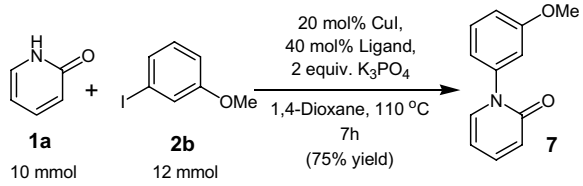
To test whether this coupling reaction could be scaled up to gram quantity, we have carried out the coupling reaction of pyridin-2-one **1a** and 3-iodoanisole **2b** on a 10 mmol scale (Scheme 2).[16] The coupling product **7** was obtained in 75% yield, which was comparable to the 1 mmol scale reaction (84% yield, Table 1).

In conclusion, we have explored the copper-catalyzed coupling reaction of pyridin-2-ones with aromatic halides based on Buchwald's protocol. This reaction has the potential to scale up to a preparative scale. It gave excellent yields with representative substituted pyridin-2-ones and aryl halides containing either electron-donating or electron-withdrawing substituents. Nonnitrogen containing heterocyclic bromides such thiophene were well tolerated. However, a strong electron-withdrawing substitutent such as a nitro group at the 5-position of the pyridin-2-one **1h** and a substituent next to the reactive centers on the pyridin-2-one **1g** or the aryl halide **2f** impeded the coupling reaction.

Table 3. Coupling reaction with heterocyclic bromides



Het-Br	% Yield
	81
	80
	27
	16
	10
	8



Scheme 2.

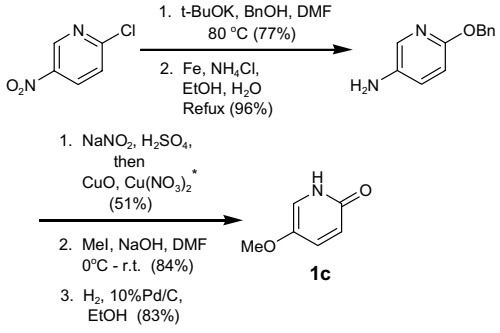
Acknowledgements

We are thankful to NSERC for an Undergraduate Student Research Award to Darryl D. Dixon and Dr. Cameron Black for suggestions on the manuscript.

References and notes

1. A few examples from the patent literature: (a) Farnesyltransferase inhibitor from Merck & Co., Inc. WO9828980; (b) α-Amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor modulator from Eisai Co. Ltd., WO0196308; (c) p-38 MAP kinase inhibitor from Celltech R&D Ltd., WO03033502 and from Bayer AG, WO03076405; (d) Factor Xa antagonist from Merck Patent GmbH, WO0040583.
2. For a review on copper-assisted nucleophilic substitution of aryl halides: Lindley, J. *Tetrahedron* **1984**, *40*, 1433–1456.
3. Renger, B. *Synthesis* **1985**, 856–860.
4. Sugahara, M.; Ukita, T. *Chem. Pharm. Bull.* **1997**, *45*, 719–721.
5. (a) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. P. *Synlett* **2000**, 674–676; (b) Lam, P. Y. S.; Vincent, G.; Clark, C. G.;

Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415–3418.
6. Mederski, W. W. K. R.; Lefort, M.; Germann, M. *Tetrahedron* **1999**, *55*, 12757–12770.
7. Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729.
8. Mallesham, B.; Rajesh, B. M.; Reddy, P. R.; Srinivas, D.; Trehan, S. *Org. Lett.* **2003**, *5*, 963–965.
9. Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428.
10. All reported yields were based on isolated products, which gave satisfactory ^{1}H NMR and MS data.
11. In contrast, the copper-catalyzed coupling reaction of **1h** with 4-methylphenylboronic acid gave 38% yield of coupling product, Ref. 6.
12. The copper-catalyzed coupling reaction of **1g** also failed with 4-methylphenylboronic acid, Ref. 6.
13. **1c** was prepared according to the following scheme:



*Decomposition of the diazonium salt was performed with the conditions reported by Cohen: Cohen, T.; Dietz, A. G.; Miser, J. R. *J. Org. Chem.* **1977**, *42*, 2053–2058.
14. Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14844–14845.
15. Ukita has also observed poorer reaction with 3-bromopyridine, Ref. 4.
16. To a 50 mL round-bottomed flask was added pyridin-2-one **1a** (0.95 g, 10 mmol), 3-iodoanisole **2b** (2.81 g, 12 mmol), CuI (0.4 g, 2 mmol), and 1,4-dioxane (15 mL). The mixture was stirred for 5-10 min to dissolve **1a** and **2b**. *N*,*N*′-dimethylethylenediamine (0.44 mL, 4 mmol) was added, followed by K_3PO_4 (4.25 g, 20 mmol). The mixture was flushed with N_2, equipped with a reflux condenser, and heated on a 110 °C bath for 7 h. After cooling to room temperature, the mixture was diluted with H_2O, extracted with EtOAc (3×). The EtOAc extracts were combined, washed with brine, dried ($MgSO_4$), and concentrated. Chromatography over silics gel and elution with hexanes–EtOAc (1:1), followed by 100 % of EtOAc gave 1.5 g (75%) of the coupling product **7**. ^{1}H NMR (acetone-d_6) δ 7.52 (1H, d, $J = 6.8$ Hz), 7.44 (1H, dt, $J = 8.8$, 1.9 Hz), 7.39 (1H, t, $J = 8.0$ Hz), 6.99–6.94 (m, 3H), 6.43 (1H, d, $J = 9.2$ Hz), 6.25 (1H, t, $J = 6.7$ Hz), 3.83 (s, 3H); MS (+ESI) m/z 202 (MH^+).