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A versatile copper-catalyzed coupling reaction of pyridin-2(1*H*)-ones with aryl halides

Kevin J. Filipski,[a,*] Jeffrey T. Kohrt,[a] Agustin Casimiro-Garcia,[a] Chad A. Van Huis,[a] Danette A. Dudley,[a] Wayne L. Cody,[a] Christopher F. Bigge,[a] Shrilakshmi Desiraju,[b] Shaoyi Sun,[b] Samarendra N. Maiti,[b] Mohamad R. Jaber[c] and Jeremy J. Edmunds[a]

[a]*Pfizer Global Research and Development, Michigan Laboratories, 2800 Plymouth Road, Ann Arbor, MI 48105, USA*
[b]*Naeja Pharmaceutical Inc., 4290-91A Street, Edmonton, Alberta, Canada, T6E 5V2*
[c]*PharmAgra Labs Inc., 40 McLean Rd, Brevard, NC 28712, USA*

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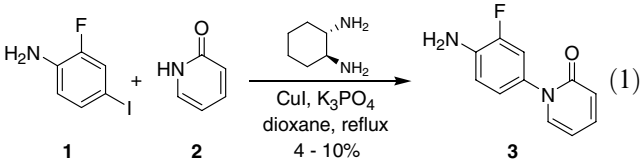
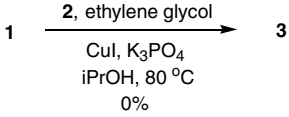
Abstract—A robust method has been developed to couple a wide variety of pyridin-2-ones and aryl halides. This C–N bond forming reaction makes use of catalytic copper(I) iodide and the ligand 8-hydroxyquinoline. These conditions tolerate a wide degree of functionality on both the aryl halide and pyridin-2-one reactants and have resulted in numerous examples being synthesized.

In recent years there have been significant improvements in the utility of carbon–nitrogen bond-forming reactions. Several published reviews detail the recent progress of copper-mediated coupling reactions for C–N bond formation.[1] Key to these improvements has been the work of Buchwald and co-workers on the use of catalytic copper in the presence of diamino ligands for the reaction of amines, amides, and nitrogen heterocycles with aryl halides.[2] Buchwald and co-workers have also effectively used palladium catalysis to effect C–N bond formation[3] and more recently reported room temperature copper-catalyzed C–N coupling reactions of amines using diketones as ligands.[4]

An important class of these C–N bond formation reactions is that involving pyridin-2-ones and aryl partners. Previous reports related to this type of coupling have appeared in the literature. Renger has used freshly prepared Cu/SiO_2 to react 2-hydroxypyridine with aryl bromides.[5] Ukita and Sugahara have published on the reaction of pyridin-2-ones and other similar nitrogen heterocycles with aryl halides using catalytic copper(I) iodide without a ligand present.[6] Lam and Mederski have developed conditions for the arylation of pyridin-2-one with phenyl boronic acids.[7] Lam et al. has also published on the use of a phenylstannane for this type of transformation.[8] Avoiding the use of boronic acids and stannanes, Li and later Leung reported on the use of copper-catalyzed Buchwald-like conditions to couple pyridin-2-ones with aryl halides and heterocyclic bromides.[9] Also, Cristau et al. has reported on the coupling of phenyl halides with nitrogen heterocycles, including 2-hydroxypyridine, using Schiff bases as ligands.[10] More recent work by Mukaiyama and co-workers uses aryl organobismuth(V) reagents for the N-arylation of pyridin-2-ones and related heterocycles.[11] Alternatively, Li and Hu have demonstrated an alternative use of Buchwald-like conditions to form substituted lactams via the intramolecular vinylation of amides.[12]



1 2 3 (1)



(2)

In our research we desired a variety of intermediates that resulted from the reaction of substituted pyridin-2-ones

* Corresponding author. Tel.: +1 734 622 1374; fax: +1 734 622 3909; e-mail: kevin.filipski@pfizer.com

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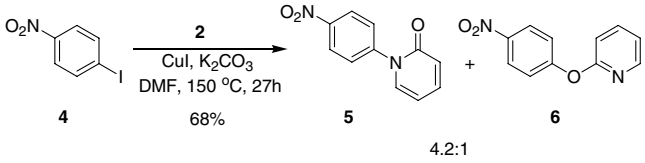
and similar nitrogen heterocycles with halo-substituted anilines and related heterocycles. Although we previously used Buchwald's conditions to successfully couple halo-substituted anilines with lactams, these conditions, as well as Buchwald's conditions using ethylene glycol as a ligand,[13] did not translate for use with pyridin-2-ones as coupling partners (Eqs. 1 and 2, respectively). Also, in our hands the ligand-free conditions of Ukita gave both C–O and C–N bond formation (Eq. 3).



(3)

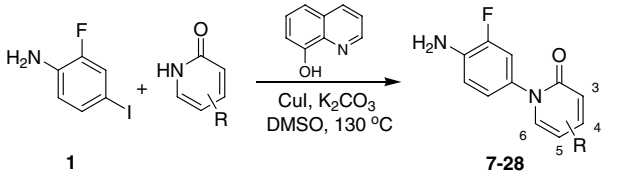
Herein, we report on general conditions, complementary to those already published that broaden the range of C–N bond-forming reactions to the additional partners of halo-substituted anilines and halo-substituted aminopyridines as well as some uniquely substituted pyridin-2-ones. These conditions are suitable for medicinal chemistry where a wide diversity of products is desired.

A search of the chemical literature yielded a list of potential conditions and ligands that could be used to perform C–N cross-coupling reactions.[14] Experimentation identified the ligand 8-hydroxyquinoline in the presence of potassium carbonate, and catalytic copper(I) iodide in DMSO, at 130 °C as being suitable for the coupling of a diverse group of pyridin-2-ones and halo-partners.[15] This ligand had been previously used in the copper-catalyzed reaction of 2-bromoanilines with alkoxides to form aryl ethers[14] and the reaction of anilines and imidazoles to form biaryl species.[16]

Table 1 shows a wide variety of pyridin-2-ones arylated with 2-fluoro-4-iodoaniline using the herein reported conditions. Pyridin-2-ones substituted at all but the 6-position participated well in this reaction. As observed with Li's conditions, the poor yields of 6-methyl **11** and 6-chloro **14** are most likely due to steric effects.

Noteworthy is the wide variety of functionalized pyridin-2-ones that are tolerated under these conditions. Pyridin-2-ones substituted by keto, ester, amino, halo, alkoxy, and thio groups all coupled well under these conditions. Interestingly, 3-acetoxypyridin-2-one did not yield the desired product **23**. It was hypothesized that under these reaction conditions, the acetate was cleaved to the free hydroxyl compound, which subsequently did not participate in the coupling reaction as was shown for derivative **17**. The *t*-butoxy carbonyl (Boc) group of compound **26** also was not tolerated under these conditions and generated the deprotected amine as major product likely due to the thermal instability of this moiety. Also, as observed by Li, 3-nitropyridin-2-one coupled to give **24** in a poor yield most likely due to the electronic effects reducing the nucleophilicity of the pyridin-2-one nitrogen.

Table 1. Reaction of substituted pyridin-2-ones with 2-fluoro-4-iodoaniline



1 **7-28**

	R	Yield[19] (%)
7	H	62
8	3-Me	78
9	4-Me	81
10	5-Me	81
11	6-Me	6
12	3-F	31
13	3,5-DiF	58
14	6-Cl	0
15	4-OMe	74
16	3-CF_3	30
17	3-OH	0
18	3-OPMB	55
19	3-OC_2H_4OBn	49
20	3-SEt	51
21	3-COPh	47
22	5-CO_2Et	50
23	3-OAc	0
24	3-NO_2	4
25	3-NH_2	38
26	3-NHBoc	2[a]
27	3-N(Me)PMB	60
28	4-$NCPh_2$	44

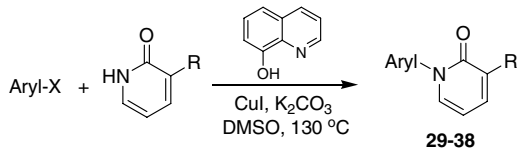
[a] The deprotected amine, **25**, was isolated as major product in 14% yield.

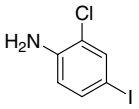
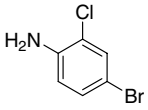
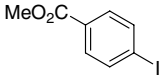
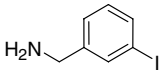
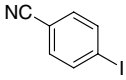
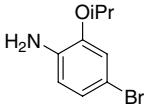
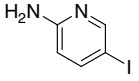
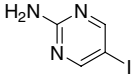
Table 2 explores the reaction of differently functionalized aryl halides with pyridin-2-ones using these conditions. Both aryl iodides and aryl bromides can be used, with the former providing superior yields (compare **29** and **30**). Electron-rich and electron-poor aryl halides both resulted in adequate yields of products. Ester, aniline, nitrile, alkoxy, nitro, and halo groups are all well tolerated. Also, heterocyclic halides like pyridines to form **36** and **37** and pyrimidine to give **38** coupled under these conditions.

Other nitrogen heterocycles also participated successfully in this reaction using the conditions reported. Table 3 shows the yields received for the reaction of several fused-ring nitrogen heterocycles. Interestingly, coupling products **42**[17] and **43** formed in good yields. The steric hindrance problems observed with 6-substituted pyridin-2-ones did not translate to these fused examples. Unexpectedly, 3-isoquinolinone **44** reacted through the oxygen instead of the nitrogen to form a biaryl ether.

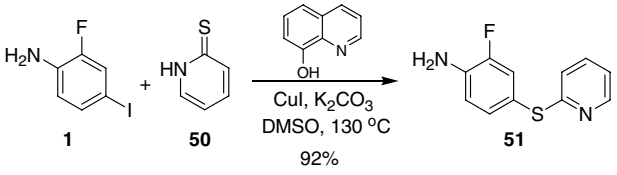
Table 3 also summarizes the reactions of several non-fused nitrogen heterocycles. Pyrazinone **46**, pyrimidin-4(3*H*)-one **47**,[18] pyridazinone **48**, and triazinone **49** all

Table 2. Reaction of pyridin-2-ones with aryl halides



	Aryl-X	R	Yield (%)
29		H	31
30		H	11
31		H	22
32		Me	37
33		Me	58
34		H	56
35		H	41
36		H	46
37		H	59
38		H	16

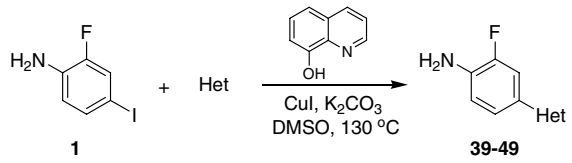
formed in good yields. One example that did not proceed under these conditions was pyrimidin-2(1*H*)-one, which failed to produce **45**.

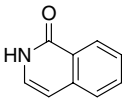
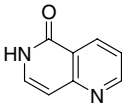
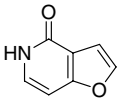
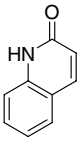
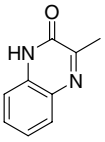
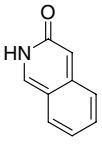
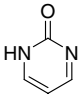
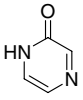
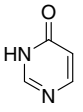
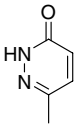
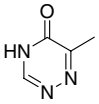


(4)

Eqs. 4 and 5 show that these conditions did not extend to thiopyridones or naphthyridinamines. Pyridine-2(1*H*)-thione **50** reacted through sulfur instead of nitrogen to form thioether **51** (Eq. 4). Likewise, 1,7-naphthyridin-8-amine **52** reacted through the exocyclic

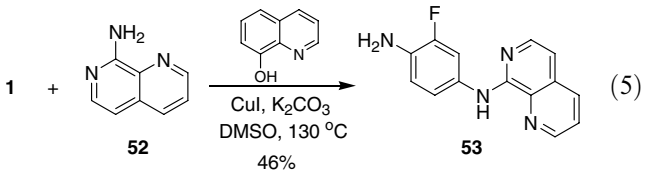
Table 3. Reaction of nitrogen heterocycles with 2-fluoro-4-iodoaniline



	Het	Yield (%)
39		66
40		76
41		92
42		54
43		40
44		0[a]
45		0
46		43
47		28
48		59
49		22

[a] Coupling through the oxygen forms the biaryl ether.

nitrogen rather than the ring nitrogen to form an amine (Eq. 5).



(5)

In conclusion, a robust method for the coupling of a variety of aryl halides with pyridin-2-ones and similar nitrogen heterocycles has been reported. The coupling products of halo-anilines and halo-substituted amino heterocycles with pyridin-2-ones were accessible through these conditions. This C–N bond-forming reaction made use of catalytic CuI and the ligand 8-hydroxyquinoline. These conditions tolerated a wide degree of functionality on both partners as shown by the numerous examples synthesized and broaden the scope of C–N bond-forming reactions.

Acknowledgment

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14. Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043–5051.
15. Typical experimental procedure: 2-Fluoro-4-iodoaniline (1.0 g, 4.2 mmol), 2-hydroxy-4-methylpyridine (0.55 g, 5.1 mmol), 8-hydroxyquinoline (0.09 g, 0.63 mmol), copper iodide (0.12 g, 0.63 mmol), and potassium carbonate (0.64 g, 4.6 mmol) were combined in a round bottom flask with 5 mL DMSO under a nitrogen atmosphere and heated to 130 °C overnight. The reaction was cooled to room temperature and poured into a mixture of 10% aq ammonium hydroxide and ethyl acetate. Charcoal was added and the mixture filtered through a pad of Celite, washing with ethyl acetate. The layers were separated with the aqueous portion being back extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by silica gel chromatography gave 0.76 g (81%) of desired material **9** as a solid. ^{1}H NMR (DMSO-d_6) δ 7.42 (1H, d, $J = 7.1$ Hz), 7.03 (1H, dd, $J = 12$, 2.2 Hz), 6.81 (2H, m), 6.21 (1H, d, $J = 1.7$ Hz), 6.09 (1H, dd, $J = 6.8$, 1.7 Hz), 5.34 (2H, s), 2.13 (3H, d, $J = 0.98$ Hz); MS (AP+) m/z 219 (MH^+).
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17. Ukita reported a 0% yield for a similar reaction of iodobenzene coupling to 2-hydroxyquinoline using the ligand-free conditions.
18. Ukita reported a 0% yield for a similar reaction of iodobenzene coupling to 4(3*H*)-pyrimidone using the ligand-free conditions.
19. All reported yields were based on the isolated products, which gave satisfactory ^{1}H NMR and MS data.