ORGANIC LETTERS

2004
Vol. 6, No. 14
2433−2435

A New Synthesis of Naphthyridinones and Quinolinones: Palladium-Catalyzed Amidation of *o*-Carbonyl-Substituted Aryl Halides

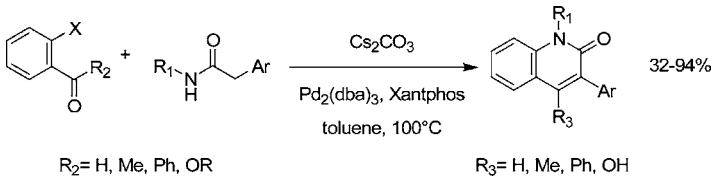
Peter J. Manley* and Mark T. Bilodeau

Department of Medicinal Chemistry, Merck & Co., Inc., P.O. Box 4, West Point, Pennsylvania 19486

peter_manley@merck.com

Received May 7, 2004

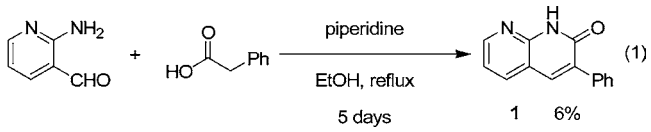
ABSTRACT

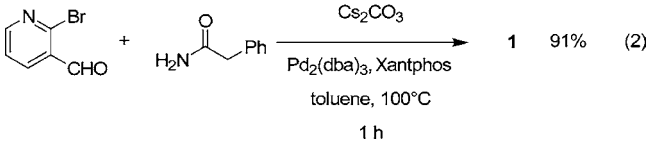


An alternative to the Friedlander condensation for the synthesis of naphthyridinones and quinolinones has been discovered. Palladium-catalyzed amidation of halo aromatics substituted in the ortho position by a carbonyl functional group or its equivalent with primary or secondary amides leads to the formation of substituted naphthyridinones and quinolinones.

In an ongoing medicinal chemistry program we required the synthesis of 3-arylnaphthyridinones and 3-arylquinolinones as key intermediates. The literature reports a number of synthetic routes to these compounds,[1] and among these the Friedlander condensation of amino aldehydes, ketones, and esters with enolizable acids and esters stands out as the most general method. The Friedlander condensation with enolizable ketones to form naphthyridines and quinolines is often performed as a single step in a single pot. However, the condensation with enolizable acids and esters to form naphthyridinones and quinolinones often requires two separate reactions to achieve the requisite bond constructions.

A number of the intermediates that we required either had not been synthesized using this methodology or gave poor yields. For example, 3-phenyl-1,8-naphthyridin-2(1*H*)-one can be synthesized in 6% yield by the Friedlander condensation of 2-aminonicotinaldehyde and 2-phenylacetic acid with catalytic piperidine in ethanol at reflux for 5 days (eq 1).[2]





As an alternative, we envisioned using a cascade sequence wherein a palladium-catalyzed cross-coupling reaction between 2-halonicotinaldehyde and 2-phenylacetamide would provide an intermediate which would then cyclize and dehydrate to give the desired naphthyridinone product. While the coupling of amides, sulfonamides, carbamates, and ureas with aryl halides has been well documented,[3−5] the presence

(1) (a) Jones, G. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., McKillop, A., Eds.; Pergamon Press: Oxford, 1984; Vol. 2, 2.08, pp 395−510. (b) Lowe, P. A. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., McKillop, A., Eds.; Pergamon Press: Oxford, 1984; Vol. 2, 2.11, pp 581−627.

(2) Hawes, E. M.; Wibberley, D. G. *J. Chem. Soc. C* **1966**, 315−321.

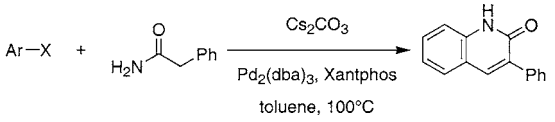
(3) (a) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043−6048 and references therein. (b)Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101−1104.

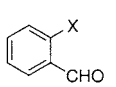
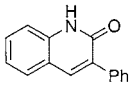
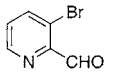
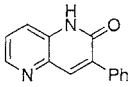
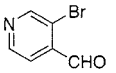
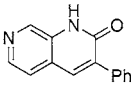
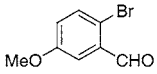
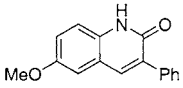
10.1021/ol049165t CCC: $27.50
Published on Web 06/11/2004

of enolizable carbonyl functionality, especially ketones, has been complicated by a competing α-arylation reaction.[6] To minimize this side reaction, we utilized the relatively mildly basic coupling conditions of Buchwald.[3] When 2-bromonicotinaldehyde and 2-phenylacetamide were combined in the presence of Cs_2CO_3, $Pd_2(dba)_3$, and xantphos[7] in anhydrous toluene at 100 °C, product **1**, the result of amide coupling and cyclodehydration, was obtained in 91% after only 1 h (eq 2). In a control experiment under identical conditions where palladium and ligand were absent, a very small amount of aldol condensation product was observed and none of the desired amide or naphthyridinone products were produced.

Given the simplicity and potential for diversity in this cascade reaction sequence, we began to investigate its scope and limitations for the synthesis of substituted naphthyridinones and quinolinones. Table 1 demonstrates the scope of the aryl halide partner. While both bromides and chlorides are effective in this reaction (entry 1), chlorides required longer reaction times than bromides (6 h versus 2 h). In addition to 1,8-naphthyridinones (e.g., **1**), 1,5- and 1,7-naphthyridinones (entries 2 and 3, respectively) could also be synthesized using this methodology. Even an electron-rich aryl bromide, as in entry 4, participated in this reaction, albeit in moderate yield.

Table 1. Tandem Pd(0)-Catalyzed Amidation/Aldol Condensation of *o*-Formyl Aryl Halides with 2-Phenylacetamide

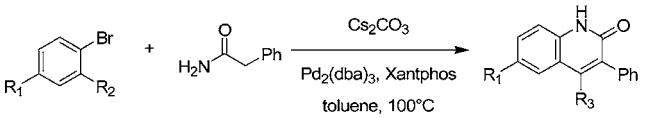


entry	Ar—X	product	yield (%)[a]
1	 X=Br Cl		X=Br 94 Cl 76
2			59
3			75
4			47

[a] Isolated yields of compounds which were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS.

The reaction was not limited to *o*-halo aldehydes. Other carbonyl or equivalent substituents were successful in this reaction (Table 2). The enolizable methyl ketone 2-bromoacetophenone gave the desired 4-methyl-substituted quinolinone (entry 1) without producing any α-arylation products. 2-Bromobenzophenone gave the 4-phenyl-substituted quinolinone (entry 2) in good yield. Coupling of methyl 2-bromobenzoate or methyl 2-bromo-5-phenylbenzoate (entries 3 and 4) with 2-phenylacetamide gave the 4-hydroxyquinolinone derivatives. 2-Bromobenzonitrile (entry 5) coupled with 2-phenylacetamide to give the 4-aminoquinolinone derivative in moderate yield. For ester and nitrile substrates (entries 3−5), after the initial cross-coupling reaction was complete (as determined by LC/MS) overnight heating of the reaction was required to affect the cyclization step.

Table 2. Tandem Pd(0)-Catalyzed Amidation/Aldol Condensation of *o*-Keto, Carboxy, and Cyano Aryl Halides with 2-Phenylacetamide



entry	R_1	R_2	R_3	yield (%)[a]
1	H	COMe	Me	65
2	H	COPh	Ph	55
3	H	CO_2Me	OH	33[b]
4	Ph	CO_2Me	OH	74[b]
5	H	CN	NH_2	52[b]

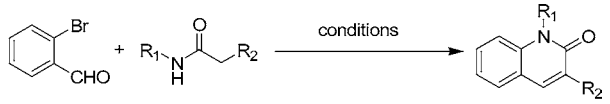
[a] Isolated yields of compounds which were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS. [b] After initial cross-coupling, the reaction mixture was heated to reflux.

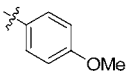
Next, we turned our attention to the amide coupling partner (Table 3). Primary aryl and heterocyclic acetamides worked well (entries 1−3) with the exception of 2-pyridylacetamide which failed to couple using our standard conditions. Employing the procedure of Buchwald[8] for the use of catalytic CuI and *N*,*N*′-dimethylethylenediamine to couple amides with aryl halides at 150 °C in a sealed tube, we were able to synthesize 3-pyridin-2-ylquinolin-2(1*H*)-one in 62% isolated yield (entry 4). The secondary amide *N*-methyl-2-phenylacetamide participated in the palladium-catalyzed reaction in good yield (entry 5); however, this seemed to be the limiting case. Neither the more sterically demanding *N*-isopropyl-2-phenylacetamide nor the *N*-arylamide *N*-phenyl-2-phenylacetamide was coupled with 2-bromobenzaldehyde using our standard conditions. Other palladium-derived catalyst systems known to couple sterically demanding cyclic carbamates[5] were investigated without success. The coupling of *N*-phenyl-2-phenylacetamide with 2-bromobenzaldehyde to form 1,3-diphenylquinolin-2(1*H*)-one was achieved using the copper methodology described above albeit in low yield (entry 6). *N*-Isopropyl-2-phenylacetamide failed to couple under every set of conditions that were investigated.

In an effort to further the scope of this reaction, primary and secondary alkyl amides were subjected to the standard

(4) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. N.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580.
(5) Ghosh, A.; Sieser, J. E.; Riou, M.; Cai, W.; Rivera-Ruiz, L. *Org. Lett.* **2003**, *5*, 2207−2210 and references therein.
(6) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360−1370 and references therein.
(7) 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene.
(8) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421−7428 and references therein.

Table 3. Tandem Pd(0)-Catalyzed Amidation/Aldol Condensation of 2-Bromobenzaldehyde with Acetamides



entry	method[a]	R_1	R_2	yield (%)[b]
1	A	H		91
2	A	H		59[c]
3	A	H		37[c]
4	B	H		62
5	A	Me		60
6	B	Ph		33
7	A	H	OMe	51[d]
8	A	Me	Me	32[d]

[a] Method A: $Pd_2(dba)_3$/xantphos; Method B: CuI, *N*,*N*′-dimethylethylenediamine. [b] Isolated yields of compounds which were characterized by ^1H NMR, ^{13}C NMR, and HRMS. [c] 1,4-Dioxane added as cosolvent. [d] NaO-*t*-Bu in *t*-BuOH added to facilitate cyclization step.

reaction conditions. Both propionamide and 2-cyclopropylacetamide coupled with 2-bromobenzaldehyde to give the amides **4** and **5** (Figure 1) in excellent isolated yields but failed to cyclize under the reaction conditions. After isolation, attempts to cyclize **4** or **5** under a number of acidic or basic conditions failed to give the desired quinolinone products. This proved true for nearly every example that was studied. Two exceptions to this general trend were identified. 2-Methoxyacetamide could be cyclized after coupling by the addition of excess NaO-*t*-Bu in *t*-BuOH to give the desired quinolinone (entry 7). *N*-Methylpropionamide could be coupled with 2-bromobenzaldehyde in moderate isolated yield (68%) but failed to cyclize under the reaction conditions. Using the method discovered above this substrate did cyclize by the addition of NaO-*t*-Bu in *t*-BuOH to give the desired quinolinone (entry 8) in low yield. Alkyl amides containing a strong electron-withdrawing substituent, such as ethyl 3-amino-3-oxopropanoate and 2-cyanoacetamide, also failed in this reaction.

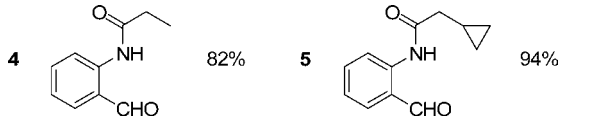


Figure 1. Compounds **4** and **5**.

In summary, we have developed an alternative strategy for the synthesis of 3-aryl naphthyridinones and quinolinones using a palladium-catalyzed cross-coupling reaction between enolizable primary and secondary amides and *o*-carbonyl substituted aryl halides. It has the advantage of being a convergent one-pot cascade sequence rather than one which often requires multiple steps. Another attractive feature of this methodology is the broader availability of *o*-carbonyl-containing aryl halides versus their amino or nitro counterparts.

Acknowledgment. We thank Dr. Art Coddington, Dr. Charles W. Ross, Dr. Harri Ramjit, and Joan S. Murphy for mass spectral analysis.

Supporting Information Available: Experimental details and physical characterization data for quinolinones and naphthyridinones (Scheme 1, Tables 1−3, and Figure 1). This material is available free of charge via the Internet at http://pubs.acs.org.

OL049165T