ORGANIC LETTERS

2011
Vol. 13, No. 17
4604–4607

Palladium-Catalyzed Intramolecular C(sp^2)−H Amidination by Isonitrile Insertion Provides Direct Access to 4-Aminoquinazolines from *N*-Arylamidines

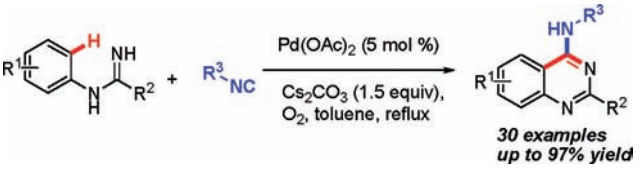
Yong Wang, Honggen Wang, Jiangling Peng, and Qiang Zhu*

State Key Laboratory of Respiratory Disease, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, 190 Kaiyuan Avenue, Guangzhou 510530, China

zhu_qiang@gibh.ac.cn

Received July 6, 2011

ABSTRACT



An efficient method for the synthesis of 4-amino-2-aryl(alkyl)quinazolines from readily available *N*-arylamidines and isonitriles via palladium-catalyzed intramolecular aryl C−H amidination by isonitrile insertion has been developed.

Transition-metal-catalyzed functionalization of C−H bonds, surrogates of preinstalled C−(pseudo)halogen bonds, serves as an attractive atom-economical and environmentally benign strategy for C−C and C−heteroatom bond formation.[1] Due to the high bond dissociation energies and ubiquity of C−H bonds in organic molecules, the presence of a nearby chelating group is usually required in order to direct positioning of a metal catalyst so that specific C−H bond activation occurs. Consequently, extra steps are required for introduction and removal of directing groups, which offset the merit of C−H functionalization and limit its synthetic applications. However, intramolecular heterofunctionalization of C−H bonds is an ideal, truly atom-economical approach to the construction of heterocyclic architectures, since heteroatoms act as both directing groups and intramolecular nucleophiles

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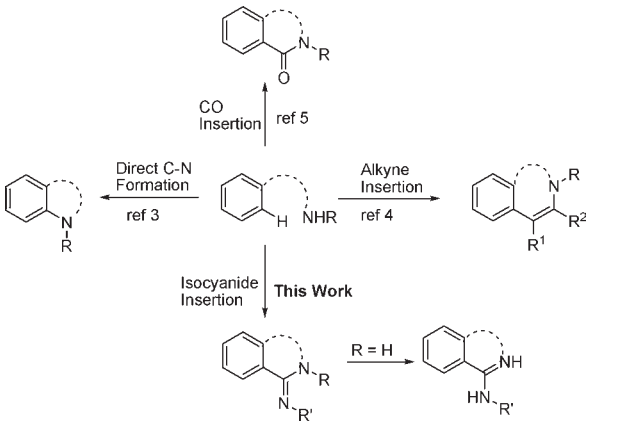
10.1021/ol201807n
Published on Web 08/05/2011

(Scheme 1).[2] A rapidly growing number of different types of heterocycles, especially those containing nitrogen, have been constructed by applying this novel strategy in recent years,[3] since the time of the seminal studies of the synthesis of carbazoles by Buchwald.[3a]

When an alkyne[4] or carbon monoxide[5] is present in the reaction mixture, coordination to the metal is followed by insertion into the carbon−metal bond prior to reductive elimination following C−H bond activation. These processes result in the formation of new carbon−metal bonds as part of expanded metallocycles. Finally, reductive elimination then furnishes diversified heterocyclic scaffolds (Scheme 1). The similarity between CO and isonitriles in terms of their coordination to transition metals[6] suggests that an equivalent C−H isonitrile insertion process should be viable. To our surprise, a transition-metal-catalyzed intramolecular C−H amidination reaction involving isonitrile insertion has not been reported, even though palladium-catalyzed inter- or intramolecular amidinations of aryl or vinyl bromides[7] and ketimine formation by C−H isonitrile insertion are known.[6a]

4-Aminoquinazolines have a privileged structure that exists in many biologically active compounds, including protein kinase inhibitors,[8] chemokine receptor CCR4 antagonists,[9]adenosine receptor antagonists,[10] and most importantly anticancer agents.[11] However, current methods for synthesis of members of this family are generally inefficient. For example, the most common approach to these substances consists of nucleophilic substitution reactions of aryl or alkyl amines with 4-chloroquinazolines, whose preparation requires multistep routes from uncommon 2-aminobenzoic acid derivatives.[12] Inaddition, this approach is inefficient for sterically hindered aryl and alkyl amines.[13]

Scheme 1. Nitrogen Heterocycles via Intramolecular C(sp^2)−H Activation



Stimulated by the results of recent studies of benzimidazole synthesis by way of C−H activation of *N*-arylamidines,[3c,d] we reasoned that isonitrile insertion would occur before reductive elimination, yielding 4-aminoquinazolines upon tautomerization. Below, we describe the first example of palladium-catalyzed intramolecular aryl C−H amidination by isonitrile insertion to provide a wide variety of 4-aminoquinazolines from *N*-arylamidines.

The effort was initiated by studies of reactions using *N*-phenylbenzamidine **1a**[14] and *tert*-butylisonitrile **2a** (3 equiv) as substrates in the presence of a palladium catalyst under various conditions (Table 1). Importantly, the desired product *N*-*tert*-butyl-4-amino-2-phenylquinazoline **3a** was produced in 42% yield under conditions involving $Pd(OAc)_2$ (10 mol %), K_2CO_3 (1.5 equiv), and benzoquinone (BQ, 1.5 equiv) in refluxing toluene (entry 1, Table 1). Screening of other oxidants used widely in palladium-catalyzed C−H functionalization methods led to the significant finding that the reaction proceeds equally well under an air atmosphere (entries 2−4, Table 1). The isolated yield of **3a** is improved to 80% when the reaction is performed under the balloon pressure of dioxygen (entry 5, Table 1).[15] The type of base used is also an important

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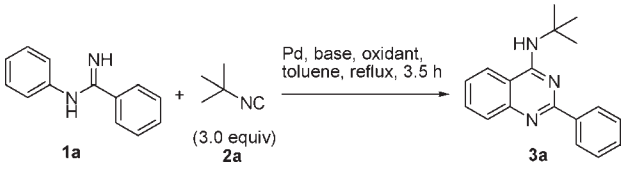
factor governing the yield of **3a**. Among those examined, the more basic Cs_2CO_3 proved to be the best base in a reaction that generated **3a** an 89% yield (entries 6–8, Table 1). Moreover, the efficiency of the reaction is nearly completely maintained when the loading of $Pd(OAc)_2$ was reduced to 5 mol %. Impressively, the product **3a** is obtained in 72% yield even when 2.5 mol % of $Pd(OAc)_2$ is employed (entries 9–10, Table 1). However, the yield of **3a** is dramatically reduced (74%) when the amount of Cs_2CO_3 is lowered to 1.0 equiv.

Table 1. Optimization of the Reaction Conditions[a]

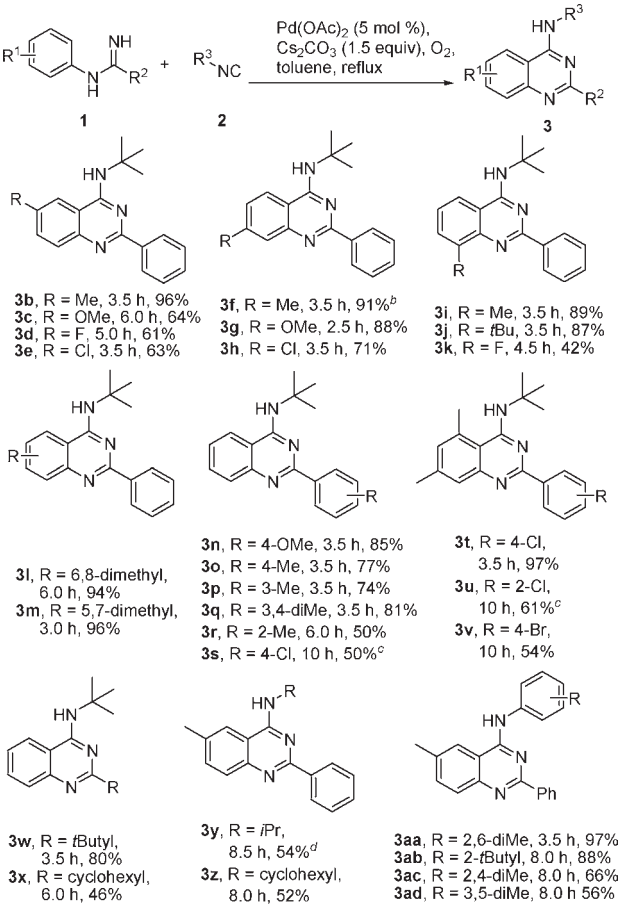


entry	catalyst (equiv)	base (equiv)	oxidant	yield (%)[b]
1[c]	$Pd(OAc)_2$ (0.1)	K_2CO_3 (1.5)	BQ	42
2[c]	$Pd(OAc)_2$ (0.1)	K_2CO_3 (1.5)	$K_2S_2O_8$	54
3[c]	$Pd(OAc)_2$ (0.1)	K_2CO_3 (1.5)	Oxone	44
4	$Pd(OAc)_2$ (0.1)	K_2CO_3 (1.5)	Air	40
5	$Pd(OAc)_2$ (0.1)	K_2CO_3 (1.5)	O_2	80
6	$Pd(OAc)_2$ (0.1)	Cs_2CO_3 (1.5)	O_2	89
7	$Pd(OAc)_2$ (0.05)	K_3PO_4 (1.5)	O_2	76
8	$Pd(OAc)_2$ (0.05)	Pyridine (1.5)	O_2	70
9	**$Pd(OAc)_2$ (0.05)**	**Cs_2CO_3 (1.5)**	**O_2**	**85**
10[d]	$Pd(OAc)_2$ (0.025)	Cs_2CO_3 (1.5)	O_2	72
11	$Pd(OAc)_2$ (0.05)	Cs_2CO_3 (1.2)	O_2	82
12	$Pd(OAc)_2$ (0.05)	Cs_2CO_3 (1.0)	O_2	74

[a] The reaction was carried out in a 0.4 mmol scale of **1a**, *tert*-butylisocyanide (1.2 mmol), palladium catalyst, base in toluene (2 mL), under balloon presure of O_2 or Ar when other oxidants were applied, reflux for 3.5 h. [b] Yield of isolated **3a**. [c] 1.5 equiv of oxidant. [d] 6 h.

The scope of reactions of *N*-aryl ring (R^1) substituted benzamidines was examined using optimized conditions involving *tert*-butylisonitrile (3.0 equiv), $Pd(OAc)_2$ (5 mol %), and Cs_2CO_3 (1.5 equiv) under the balloon pressure of dioxygen in toluene at reflux. In general, various electron-donating group substituted aniline ring containing substrates react to form corresponding *N*-*tert*-butyl-4-amino-2-phenylquinazolines in excellent yields (**3b**, **3f**–**g**, **3i**–**j**, Scheme 2). An exception is found for **1c** that contains a *para*-methoxyaniline moiety, which reacts to form **3c** in only a 64% yield. In sharp contrast, benzamidine reactants with electron-withdrawing group (eg., F and Cl) substituted aniline rings react inefficiently (42–71%) (**3d**–**e**, **3h**, **3k**, Scheme 2). This observation suggests that an electrophilic aromatic substitution (S_EAr) reaction pathway might be involved in C(sp^2)–H bond activation. It is noteworthy that *meta*-methyl substituted **1f** produces two regioisomeric products in near equal amounts, while reactions of the methoxy and chloro analogs take place with complete regioselectivity (**3g**–**h**). Notably, the bulky neighboring *tert*-butyl group in **3j** does not hamper the cycloinsertion reaction and two methyl groups on the benzamidine aniline ring were found to have a synergistic effect on the yield (**3l**–**m**).

Scheme 2. Substrate Scope for the Synthesis of Substituted 4-Amino-2-Substituted Quinazolines[a]



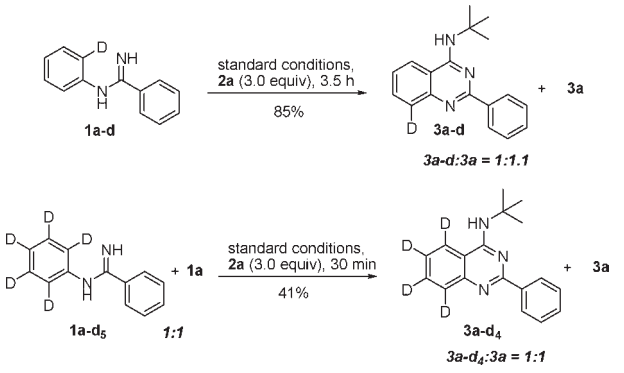
[a] Reaction conditions: **1** (0.4 mmol), isonitrile **2** (1.2 mmol), $Pd(OAc)_2$ (5 mol %), Cs_2CO_3 (1.5 equiv), toluene (2 mL), O_2 balloon at reflux, yield of isolated **3**. [b] A 1:1 mixture of 5-methyl and 7-methyl substituted isomers was obtained. [c] *tert*-Butylisonitrile **2a** (2.0 mmol) and $Pd(OAc)_2$ (10 mol %) were applied. [d] Isopropylisonitrile (5.0 equiv) was applied.

Benzamidine ring (R^2) substituent effects on the intramolecular aryl C–H amidination by isonitrile insertion was also explored. The results show that electron-donating substituents on this aryl ring undergo more favorable reactions than do their electron-withdrawing group substituted counterparts (see formation of **3n**–**3q** vs **3s**). This trend suggests that the electron density on the amidine nitrogen is crucial in complexation with the palladium catalyst. However, the efficiencies of the reactions are highly sensitive to ortho-substituents, a probable result of interference with coordination of the amidine nitrogen to the palladium catalyst (**3r**, 50% vs **3o**, 77% and **3p**, 74%). In addition, reactions of the substrates containing chloro (**3t**, 97%) or bromo (**3v**, 54%) take place with high or modest efficiency, which

can be used for further elaboration. In addition, 2-alkyl substituted 4-aminoquinazolines **3w**−**3x** are also generated by using the new methodology.

Finally, the scope of the process with respect to the isonitrile reactant was examined. Reactions of isopropyl and cyclohexyl isonitrile are less efficient than those of *tert*-butylisonitrile as reflected by the fact that the corresponding *N*-alkyl-4-amino-2-phenyl-quinazolines **3y**−**3z** are formed in much lower yields (52−54%). The sterically hindered aryl isonitriles **3aa**−**3ab** participate in higher yielding processes than their less hindered counterparts **3ac**−**3ad**, a result that correlates with the thermal stabilities of the isonitriles. In addition, the reaction of thermally unstable phenyl isonitrile does not produce the corresponding quinazoline product. Considering the poor reactivity of sterically hindered amines in nucleophilic substitution reactions with 4-chloroquinazolines,[12] the current method affords a more efficient approach to produce 4-aminoquinazoline derivatives with bulky groups on the C-4 nitrogen.

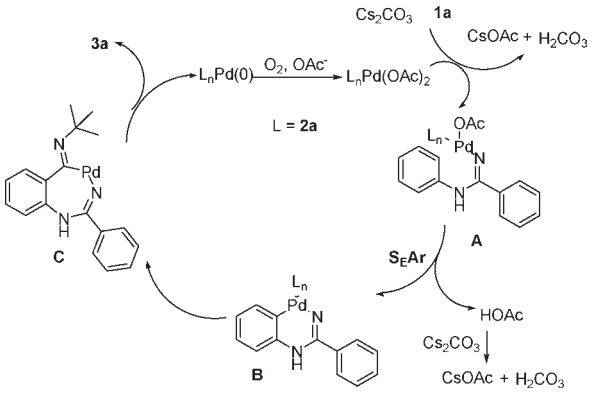
Scheme 3. Deuterium Isotope Effect Studies



To gain insight into the mechanism of this reaction, both intra- and intermolecular kinetic isotope effects were determined by using the respective monodeuterated *N*-phenylbenzamidine **1a-d** and pentadeuterated *N*-phenylbenzamidine **1a-d$_5$** (Scheme 3). No kinetic isotope effects were observed in reactions of these substrates, indicating that aromatic C−H cleavage is not involved in the rate-determining step.

Based on the observations made in this effort, the reaction mechanism shown in Scheme 4 appears to be plausible. In the route, coordination of the amidine nitrogen with isonitrile-ligated Pd(II) aided by Cs_2CO_3 leads to formation of complex **A**. Electrophilic substitution on the *N*-aryl amidine ring then provides the cyclopalladation intermediate **B**, which undergoes migratory insertion of the isonitrile. Subsequent reductive elimination of the resulting cyclic imidoyl palladium intermediate **C** followed by tautomerization delivers product **3a** with concurrent formation of a Pd(0) species, which is reoxidized to Pd(II) by dioxygen.

Scheme 4. Plausible Reaction Mechanism



In conclusion, the investigation described above has led to the development of a new palladium-catalyzed intramolecular aryl C−H amidination reaction that occurs through isonitrile insertion. The process generates 4-amino-2-aryl(alkyl) quinazolines with a broad substrate scope and good functionality tolerance from readily available *N*-arylamidines and isonitriles in a concise, efficient, and atom-economic manner. Sterically hindered groups, such as *tert*-butylamino and 2,6-dimethylphenylamino, can be introduced at the C-4 position of the quinazoline ring system, which is a privileged scaffold that exists in many biologically active molecules. The reaction conditions used are relatively mild and environmentally benign. Owing to the fact that the newly developed method employs structurally rich and readily available isonitriles, it can be applied in approaches for diversity oriented construction of nitrogen containing heterocycles.

Acknowledgment. We are grateful to the National Science Foundation of China (21072190) for financial support of this work.

Supporting Information Available. Experimental procedure, and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.