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Facile Synthesis of 2-Amino-3-Bromoquinolines by Palladium-Catalyzed Isocyanide Insertion and Cyclization of *gem*-Dibromovinylanilines

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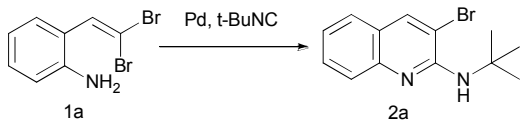
A novel and efficient synthesis of 2-amino-3-bromoquinolines through palladium-catalyzed isocyanide insertion followed by intramolecular cyclization of *gem*-dibromovinylanilines was developed. The reactions were carried out in 1,4-dioxane at 100°C for 2-3h and the corresponding products were obtained in good isolated yields.

The quinoline scaffold occurs in a large number of natural products and synthetic drugs with different biological activities[1]. Especially 2-aminoquinoline derivatives have been frequently studied during the past decades because of their pharmacological potential covering a range of possible applications, including anti-cancer[2], anti-hypertensive[3] and anti-Alzheimer's[4] activities. In the past decades, while numerous synthetic approaches have been developed for quinoline synthesis[5], only a few examples are available for the synthesis of 2-aminoqunolines[6]. Nevertheless, the existing methods generally suffer from limited availability of substrates, complicated multistep procedures and low regioselectivity in most cases. Meanwhile, aromatic halides are a very important class of compounds not only widely used in drug and natural product synthesis, but also providing good opportunities for further formation of C-C and/or C-heteroatom bonds by metal-catalyzed coupling reactions[7]. Therefore, simple and efficient new protocols for the preparation of halo-2-aminoquinolines are still desirable.

Gem-dihaloolefins as highly versatile reagents have attracted considerable attentions in transition metal-catalyzed cross-coupling chemistry due to their high reactivity and ready availability from inexpensive aldehydes[8]. Recently, a number of novel and elegant methods for the preparation of various substituted indoles from 2-(*gem*-dibromovinyl)anilines were developed via Pd and/or Cu-catalyzed tandem cross-coupling strategies, such as C-N/C-C[9, 10], C-N/C-N[11], C-N/C-P[10], C-N/C-H[12], C-N/carbonylation[13], and C-N/carbonylation/C-C reactions[14]. However, to the best of our knowledge, there is no example of constructing quinoline scaffold from *gem*-dihalovinylanilines. In our continuous studies of 1,1-dibromoolefins[15], we report herein the preparation of 2-amino-3-bromoquinoline derivatives through tandem palladium-catalyzed isocyanide insertion and intramolecular cyclization of *gem*-dibromovinylanilines. The reaction involves t-butyl isocyanide and 2-(*gem*-dibromovinyl)anilines using palladium catalysis (Scheme 1).

Scheme 1. Strategic Approach to the Synthesis of 2-Amino-3-Bromoquinolines

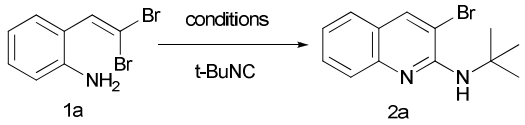


1a 2a

Our investigation started with the treatment of 2-(*gem*-dibromovinyl)aniline (**1a**) and t-BuNC in the presence of $Pd(OAc)_2$ (5 mol%) and PPh_3(10 mol%) using K_2CO_3 (2 equiv.) as the base in THF at 100°C. To our delight, the quinoline product **2a** was obtained in 70% yield after 3h (Table 1, entry 1). To improve the yield, screening of the reaction conditions was then carried out. Firstly, by using $Pd(OAc)_2$ as catalyst, the effect of different solvents including DMSO, DMF, Toluene, 1,4-dioxane and CH_3CN was studied (Table 1, entry 2-6). Among them, 1,4-dioxane gave **2a** in the highest yield (Table 1, entry 5). Lautens[16] reported a convenient synthesis of 2-bromoindoles using P*t*Bu_3. When P*t*Bu_3 was used in our studies, **2a** was obtained in 34% yield while 2-bromo indole in 29% yield. When t-BuNC (0.6eq) was used, **2a** was obtained in 17% yield, and 2-bromoindole in 33% yield (Table 1, entry 7, 8). After screening a series of palladium catalysts, $Pd(dppf)Cl_2$ turned out to be the best choice (Table 1, entry 6-12). We were delighted to find that the reaction went well without additional ligand PPh_3 (Table 1, entry 13). Other experiments with different bases showed that Cs_2CO_3 was the most efficient one (Table 1, entry 13-16). In addition, elevating or lowering reaction temperature resulted in decreased yields of **2a** (Table 1, entry 17,18). On the basis of these findings, a wide variety of 2-amino-3-bromoquinolines were prepared in good yields from 2-(*gem*-dibromovinyl)anilines under the optimized conditions: $Pd(dppf)Cl_2$ as the catalyst, Cs_2CO_3 as the base and 1,4-dioxane as the solvent at 100°C. The results are shown in Table 2.

Gratifyingly, *gem*-dibromovinylanilines bearing both electron-withdrawing and electron-donating moieties on the aromatic ring afforded the quinoline products in good yields (Table 2, entry **1**-**6**). It is obvious that the electronic effects of substituted groups on the benzene rings in 2-(*gem*-dibromovinyl)anilines had little impact on the yields of the products. Halogen substitutes on the aromatic ring were well tolerated, giving polyhalogenated 2-amino-3-bromoquinolines (Table 2, entry **7**-**10**), which provides attractive

Table 1. Optimization of the reaction conditions[a]



1a 2a

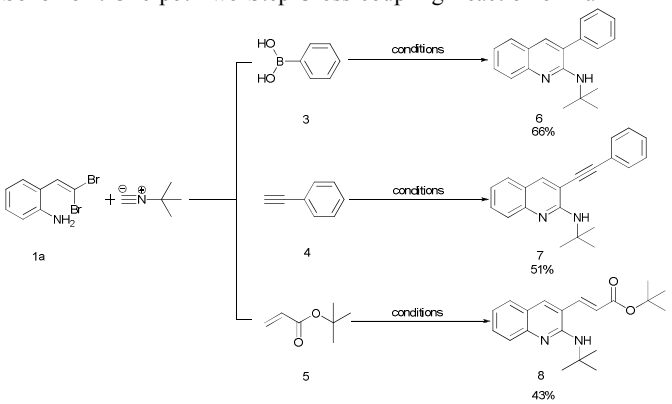
Entry	Catalyst	Ligand	Solvent	Base	Yield[b](%)
1	$Pd(OAc)_2$	PPh_3	THF	K_2CO_3	70
2	$Pd(OAc)_2$	PPh_3	DMSO	K_2CO_3	43
3	$Pd(OAc)_2$	PPh_3	DMF	K_2CO_3	46
4	$Pd(OAc)_2$	PPh_3	Toluene	K_2CO_3	51
5	$Pd(OAc)_2$	PPh_3	Dioxane	K_2CO_3	77
6	$Pd(OAc)_2$	PPh_3	CH_3CN	K_2CO_3	72
7	$Pd(OAc)_2$	$PtBu_3$	Dioxane	K_2CO_3	34
8	$Pd(OAc)_2$	$PtBu_3$	Dioxane	K_2CO_3	17[c]
9	$PdCl_2$	PPh_3	Dioxane	K_2CO_3	68
10	$Pd(PPh_3)_4$	—	Dioxane	K_2CO_3	61
11	$Pd(dppf)Cl_2$	PPh_3	Dioxane	K_2CO_3	80
12	$Pd(PPh_3)Cl_2$	PPh_3	Dioxane	K_2CO_3	79
13	$Pd(PPh_3)Cl_2$	—	Dioxane	K_2CO_3	81
14	$Pd(dppf)Cl_2$	—	Dioxane	Cs_2CO_3	86
15	$Pd(dppf)Cl_2$	—	Dioxane	Na_2CO_3	82
16	$Pd(dppf)Cl_2$	—	Dioxane	K_3PO_4	65
17	$Pd(dppf)Cl_2$	—	Dioxane	Cs_2CO_3	71[d]
18	$Pd(dppf)Cl_2$	—	Dioxane	Cs_2CO_3	58[e]

[a] Reaction conditions: **1a** (0.2 mmol), t-BuNC (0.3 mmol), base (0.4 mmol), catalyst (0.01 mmol), ligand (0.04 mmol), solvent (2.0 mL), sealed tube, 100°C, 3h. [b] isolated yields. [c] t-BuNC (0.12 mmol). [d] 120°C. [e] 80°C.

intermediates for their further transformation via transition-metal catalyzed C-C or C-heteroatom formation reactions.

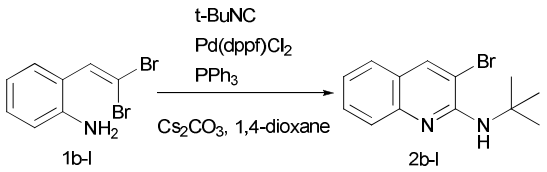
Having successfully established the general method for the synthesis of 2-amino-3-bromoquinolines, we envisioned that 2-amino-3-bromoquinolines could easily undergo an intramolecular cross-coupling reaction to afford various 3-substituted-2-aminoquinolines, even through a one-pot two-step process. As expected, we found 3-substituted-2-aminoquinolines (**6**/**7**/**8**) could be conveniently prepared in 66%/51%/43% yields through palladium-catalyzed isocyanide insertion and typical Suzuki/Sonogashira/ Heck reaction, respectively (Scheme 2).

Scheme 2. One-pot Two-Step Cross-coupling Reaction of 2a[a]

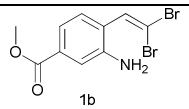
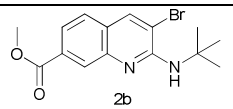
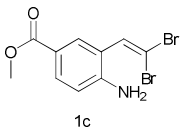
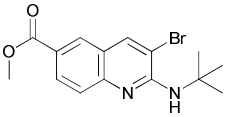
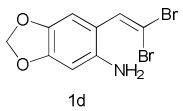
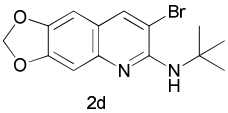
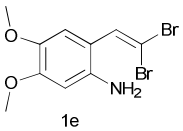
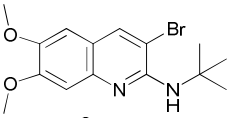
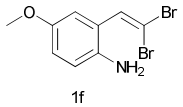
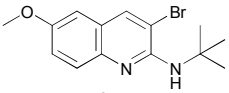
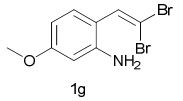
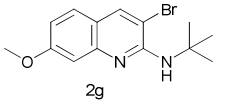
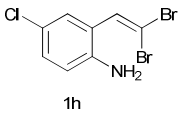
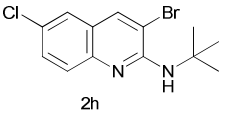
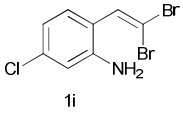
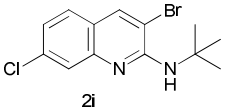
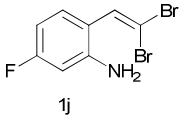
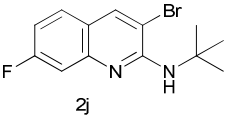
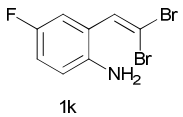
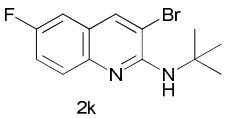
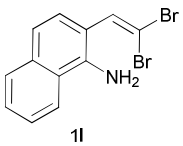
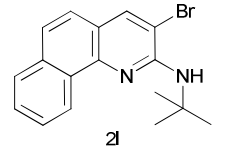


[a] Reaction conditions: step (1) **1a** (0.2 mmol), t-BuNC (0.3 mmol), Cs_2CO_3 (0.4 mmol), $Pd(dppf)Cl_2$ (0.01 mmol), 1,4-dioxane (2.0 mL), sealed tube, 100°C, 3h; step (2) **3**/**4**/**5** (0.3 mmol), K_3PO_4 (0.4 mmol), $Pd(dppf)Cl_2$ (0.01 mmol), Toluene (2.0 mL), sealed tube, 120°C, N_2, 12h.

Table 2. Synthesis of 2-amino-3-bromoquinolines 2b-2l[a]



1b-l 2b-l

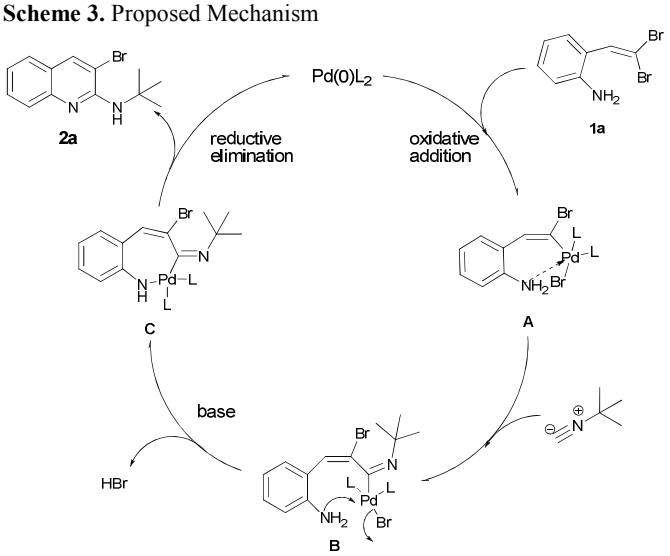
Entry	Substrate	Product	Yield[b](%)
1			82
2			87
3			85
4			81
5			84
6			86
7			80
8			82
9			83
10			84
11			85

[a] Reaction conditions: **1** (0.2 mmol), t-BuNC (0.3 mmol), Cs_2CO_3 (0.4 mmol), $Pd(dppf)Cl_2$ (0.01 mmol), 1,4-dioxane (2.0 mL), sealed tube, 100°C, 3h. [b] isolated yields

Since ortho effect exists in many metal-catalyzed reactions[6a,15,17], a plausible mechanism for the formation of 2-amino-3-bromoquinoline

is proposed in Scheme 3. Initial oxidative addition of cis-Bromovinyl of **1a** to Pd(0) species formed vinylpalladium complex **A**. Subsequent migratory insertion of t-butyl isocyanide to **A** gave intermediate **B**, followed by intramolecular nucleophilic attack of the aniline to provide intermediate **C** and hydrogen bromide. Reductive elimination of **C** afforded final product **2a**, generating the Pd(0) catalyst. Further studies into the mechanism of this transformation and synthetic applications are still ongoing.

Scheme 3. Proposed Mechanism



Conclusions

In summary, we have developed a novel and efficient method for the construction of 2-amino-3-bromoquinolines via palladium-catalyzed isocyanide insertion followed by intramolecular cyclization of gem-dibromovinylanilines. The palladium-catalyzed reactions proceeded in 1,4-dioxane at 100°C for 3h and the corresponding products were obtained in good isolated yields. More importantly, this method can be extended to the synthesis of various 3-substituted-2-aminoquinolines via palladium-catalyzed Suzuki/Sonogashira/Heck reactions starting from easily accessible *gem*-dibromovinylanilines in a one-pot two-step way.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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