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ARTICLE TYPE

A Convenient Palladium-Catalyzed Carbonylative Synthesis of Quinazolines from 2-Aminobenzylamine and Aryl Bromides

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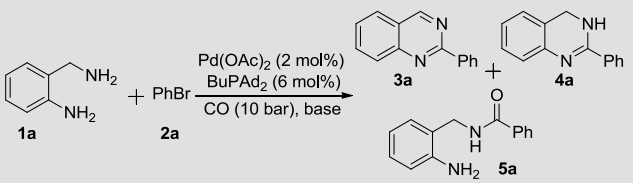
A novel and practical strategy towards quinazoline scaffolds synthesis has been achieved. Through palladium-catalyzed carbonylative coupling of 2-aminobenzylamine with aryl bromides, the desired quinazolines were produced in moderate to good yields for the first time. The reactions followed by aminocarbonylation-condensation-oxidation sequence in a one-pot one-step manner. Preliminary investigation showed DMSO serves both as solvent and oxidant in this procedure.

Palladium-catalyzed carbonylation reactions have been regarded as a subject of great synthetic toolkit in modern organic synthetic chemistry[1] and numerous efforts have been made to apply carbonylations in the synthesis of biological active compounds.[2] Among the numerous heterocyclic compounds, nitrogen-containing compounds frequently exist in natural products, agrochemicals and pharmaceuticals.[2c,3] Quinazolines and their derivatives, among these heterocycle compounds, have been defined as the privileged scaffold because they exhibit a wide spectrum of biological and pharmacological activities including anticancer,[4] antiviral,[5] antitubercular[6] and antimalarial[7] properties. Recently, Yang and co-workers reported that derivatives of quinazolines can serve as a novel potent and selective FLT3 inhibitor and possess anti-acute myeloid leukemia (AML) activities.[8] As the accepted importance, many attentions have been attracted for quinazolines preparation.[9-21] Most recent protocols toward quinazolines synthesis include the reaction between 2-aminobenzophenones and benzylamines by using supported copper oxide nanoparticles[9] or 4-HO-TEMPO[10] as the catalyst; copper-catalyzed reactions between amidines and 2-halophenyl carbonyl compounds,[11] (2-bromophenyl)methylamine,[12] or *ortho*-halobenzyl halide.[13] Copper-catalyzed Ullmann-type coupling and aerobic oxidation of (2-bromophenyl)methylamine with benzamides;[14] copper-catalyzed tandem reaction of 2-bromobenzyl bromides with aldehydes and aqueous ammonia;[15] copper-catalyzed condensation of *ortho*-bromoaryl carbonyl compounds, ammonia and aldehydes;[16] copper-catalyzed cascade reaction of (2-aminophenyl)methanol, ammonium salts and aldehyde;[17] and the condensation of 2-aminobenzylamine with aldehyde followed by subsequent oxidation by the strong oxidants such as 2,3- dichloro-5,6-dicyanobenzoquinone (DDQ), tetrachloro-1,4-benzoquinone (TCQ),[18] MnO_2,[19] or NaClO.[20] Additionally, Walton and co-workers developed microwave-promoted synthesis of quinazolines from 2-(aminoaryl)alkanone *O*-phenyl oximes and aldehydes in the presence of zinc salt.[21a,21b] In 2013, Zhang's group demonstrated a copper-catalyzed annulation of amidines for the quinazoline synthesis through C-H activation.[21c] However, to the best of our knowledge, no carbonylative approach has been exploited for the preparation of quinazolines until nowadays. In our continuing efforts to manifest useful carbonylative reactivity profiles in this area,[22] herein we wish to report the first carbonylative protocol towards quinazoline preparation with readily available aryl bromides and 2-aminobenzylamine as starting materials.

We initiated the optimization with 2-aminobenzylamine and bromobenzene as the model substrates in the present of $Pd(OAc)_2$ (2 mol%) and $BuPAd_2$ (6 mol%) under 10 bar of CO with Et_3N as the base in DMAc at 120 °C. Only few amounts of the desired product were formed with 8% of the intermediate **4a** and non-cyclized compound **5a** as the main by-product (Table 1, entry 1). In order to accelerate the cyclization step, some Lewis acids were tested such as $FeCl_3$, $MgSO_4$, $MgCl_2$ and $CuCl_2$, but no significant improvement was got (Table 1, entries 2-5). Increasing the temperature to 140 °C, 21% of the desired product **3a** and 70% **5a** were observed (Table 1, entry 6). DBU as base shown better selectivity compared with the other tested bases (Table 1, entry 7). Some other aprotic polar solvents such as DMF, NMP and DMSO were screened as well. Among them, DMSO gave the best results (Table 1, entries 8-11). It is worthy to mention that no non-cyclized intermediate **5a** was observed when DMSO was used as the solvent and DBU as the base. The inorganic bases, taken an example of K_2CO_3 or $K_3PO_4 \cdot H_2O$ displayed commonplace performance in this system (Table 1, entries 12 and 13). To our delight, 92% isolated yield of 2-phenylquinazoline could be achieved by increasing the loading of palladium catalyst and prolong the reaction time (Table 1, entry15).

Table 1. Optimization of the reaction parameters.[a]



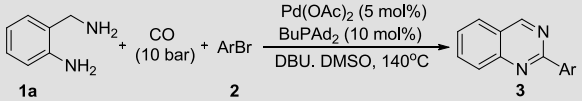
Entry	Base	Additive	Solvent	T/°C	Yield(%)[b] 3a/4a/5a
1	NEt_3	-	DMAc	120	10/8/50

2	NEt_3	$FeCl_3$	DMAc	120	14/2/45
3	NEt_3	$MgSO_4$	DMAc	120	2/1/3
4	NEt_3	$MgCl_2$	DMAc	120	11/3/44
5	NEt_3	$CuCl_2$	DMAc	120	4/0/0
6	NEt_3	-	DMAc	140	21/7/70
7	DBU	-	DMAc	140	22/25/4
8	NEt_3	-	DMF	140	17/8/46
9	NEt_3	-	DMSO	140	27/5/22
10	NEt_3	-	NMP	140	18/3/58
11	DBU	-	DMSO	140	50/31/0
12	K_2CO_3	-	DMSO	140	41/21/22
13	K_3PO_4 H_2O	-	DMSO	140	28/8/34
14	DBU	-	DMSO	140[c]	62(54)/27/0
15	DBU	-	DMSO	140[c]	(92)[d]/0/0

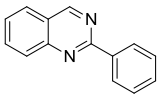
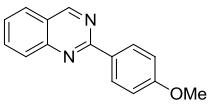
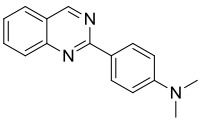
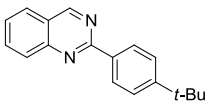
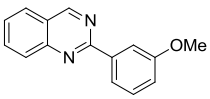
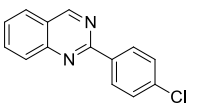
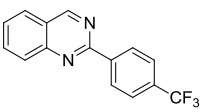
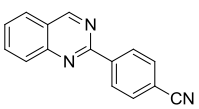
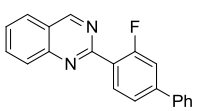
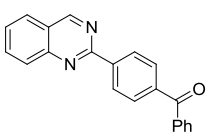
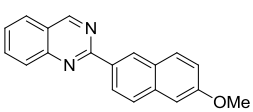
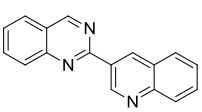
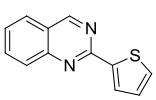
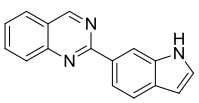
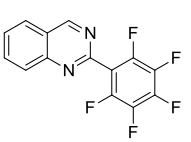
Reaction conditions: [a] **1a** (0.5 mmol, 1.0 equiv.), **2a** (0.5 mmol, 1.0 equiv.), $Pd(OAc)_2$ (2 mol%), $BuPAd_2$ (6 mol%), base (3.0 equiv.), additive (2.0 equiv.), CO (10 bar), solvent (2 mL), 17 h, indicated temperature. [b] GC yields with hexadecane as internal standard, isolated yields in parentheses. [c] 36h. $Pd(OAc)_2$ (5 mol%), $BuPAd_2$ (10 mol%). [d] 36h.

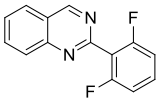
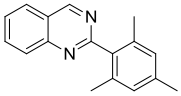
Having established the optimized system, we turned our attention to the substrates scope of this approach. As shown in Table 2, a wide range of substitutions could be tolerated under our reaction conditions and delivering the corresponding products in good to excellent yields. More specifically, aryl bromides with electron-donating substitution such as methoxy (Table 2, entries 2 and 5), dimethylamino (Table 2, entry 3), *tert*-butyl (Table 2, entry 4) all reacted with 2-aminobenzylamine to give the corresponding quinazolines in good to excellent yields. Trifluoromethyl (Table 2, entry 7) and cyano (Table 2, entry 8) as representative examples of electron-withdrawing groups worked as well in our conditions. Notably, naphthyl (Table 2, entry 11), biphenyl (Table 2, entry 9) and aryl ketone (Table 2, entry 10) bromides could be applied as substrates and succeeded to provide the corresponding products in high yields. Interestingly, heteroaryl bromides, taken the quinoline (Table 2, entry 12), thiophene (Table 2, entry 13) and indole (Table 2, entry 14) for examples, the target molecules were successfully produced in 70%, 59% and 52% yields. Unfortunately, multi fluoro substituted bromobenzene (Table 2, entries 15 and 16) did not work under our conditions. And more steric substrate such as the 2,4,6-trimethylbromobenzene failed in this process (Table 2, entry 17).

Table 2. Substrates scope for the quinazolines synthesis.[a]



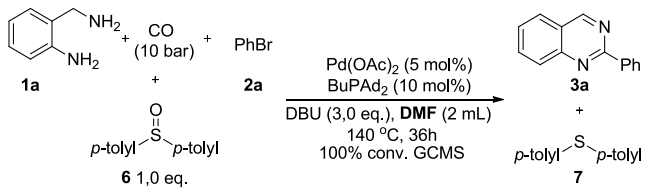
1a 2 3

Entry	Product	Yield[b]
1		92%
2		91%
3		87%
4		61%
5		62%
6		78%
7		81%
8		65%
9		93%
10		72%
11		83%
12		70%
13		59%
14		52%
15		<5%

16		<5%
17		<5%

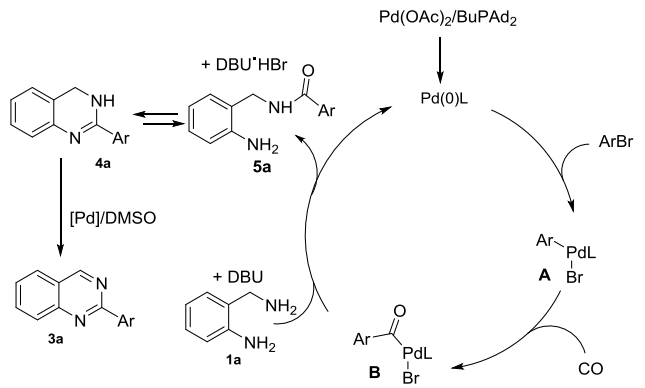
Reaction conditions: [a] **1a** (0.5 mmol, 1.0 equiv.), **2** (0.5 mmol, 1.0 equiv.), $Pd(OAc)_2$ (5 mol%), $BuPAd_2$ (10 mol%), DBU (3.0 equiv.), CO (10 bar), DMSO (2 mL), 36 h, 140 °C. [b] Isolated yield.

In order to gain some details about the mechanism, control experiment was conducted. The reaction was run in the present of 4,4'-dimethyldiphenylsulfoxide **6** with DMF as the solvent instead of DMSO (Scheme 1). The desired product **3a** and di-*p*-tolylthio ether **7** were observed with full conversion of starting materials which proven that DMSO played as oxidant in our system.



Scheme 1. Preliminary investigation.

Taken the above observations together, we proposed a most plausible reaction mechanism in Scheme 2. The reduction of Pd(II) to Pd(0) started the catalyst cycle, then was followed by the oxidative addition of aryl bromides to Pd(0) delivering the corresponding organopalladium species **A**. After the coordination and insertion of CO, the key intermediate acylpalladium complex **B** was formed. Then nucleophilic attack of **1a** to intermediate **B** took place giving the compound **5a** and Pd(0) under the assistant of base which ready for next cycle. The produced compound **5a** underwent intramolecular cyclization and produced the intermediate **4a**. Then intermediate **4a** was subsequently oxidized into the terminal quinazoline product under the assistant of palladium and DMSO.



Scheme 2. Proposed reaction mechanism.

Conclusions

In summary, a novel and practical protocol for the synthesis of quinazolines has been developed. Through palladium-catalyzed carbonylative coupling of 2-aminobenzylamine with aryl bromides, the desired quinazolines were produced in moderate to good yields. The reactions followed by aminocarbonylation-condensation-oxidation sequence in a one-pot one-step manner. Preliminary investigation shown DMSO serves both as solvent and oxidant in this procedure.

General reaction procedure: An oven-dried 12 mL vial with stir bar was charged with 2-aminobenzylamine (0.5 mmol, 1 equiv.), $Pd(OAc)_2$ (5 mol%), and $BuPAd_2$ (10 mol%). Then, aryl bromide (0.5 mmol, 1.0 equiv.), DMSO (2 mL), DBU (1.5 mmol, 3 equiv) were injected into the vial under argon flow sequentially. The vial (or several vials) was placed in an alloy plate, which was transferred into a 300 mL autoclave of the 4560 series from Parr Instruments under an argon atmosphere. After flushing the autoclave three times with CO, a pressure of 10 bar CO was adjusted at ambient temperature. The reaction mixture was heated at 140 °C for 36 h. After the reaction finished, the autoclave was cooled down to room temperature and the pressure was released carefully. The product was extracted with ethyl acetate (5 × 3 mL). The organic layers were washed with brine, dried over Na_2SO_4, and evaporated to yield the crude reaction mixture. The purification was done by combi flash machine flash chromatography on silica gel (eluent: heptanes:EtOAc = 60:40).

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An interesting approach for the synthesis of 2-functionalized quinazolines has been developed. Various aryl bromides undergo palladium-catalyzed aminocarbonylation with 2-aminobenzylamine to provide the corresponding quinazolines in moderate to excellent yields.