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Palladium-Catalyzed Dicarbonylative Synthesis of Tetracycle Quinazolinones

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An interesting procedure for the synthesis of isoindolo[1,2-*b*]quinazolin-10(12*H*)-ones has been developed. Starting commercially available 2-bromoanilines and 2-bromobenzyl amines, under the assistant of palladium catalyst, the desired products were isolated in good yields. Notably, this procedure proceeded in a highly selective manner; two molecules of CO were incorporated into the substrates selectively.

Skeleton of 4(3*H*)-quinazolinone widely exists in more than 100 naturally occurring alkaloids.[1] Because of their diverse biological and pharmacological activities and extensive applications on pharmaceutical,[2] research interest on the synthesis of 4(3*H*)-quinazolinone and its derivatives has never faded since the first report of 4(3*H*)-quinazolinone compound in 1869.[3] Among the family of 4(3*H*)-quinazolinone and its analogise, tetracycle quinazolinone (Figure 1, A) is one of the most important members. The structural unit of tetracycle quinazolinone consists in a series of biologically- or pharmacologically-active alkaloids, such as luotonin A,[4] 14-azacamptothecin[5] and rutaecarpine (Figure 1, B). Up to present, there are three typical strategies to building the structure of tetracycle quinazolinone: (i) through the condensation reaction using anthranilic acid or its derivatives as the starting materials (Scheme 1, pathways **A** and **B**);[6] (ii) by means of intramolecular aromatic hemolytic substitution (Scheme 1, pathways **C** and **D**);[7] (iii) utilizing Pd-catalyzed sequential cyanation/*N*-addition/*N*-arylation (Scheme 1, pathways **E** and **F**).[8] However there are more or less drawbacks in these methods including complex multistep procedure in the preparation of substrates, low reaction selectivity or yield and using highly poisonous reagents. Therefore searching facile and efficient protocols to construct the framework of tetracycle quinazolinones still remains a research field of undoubted current attention.

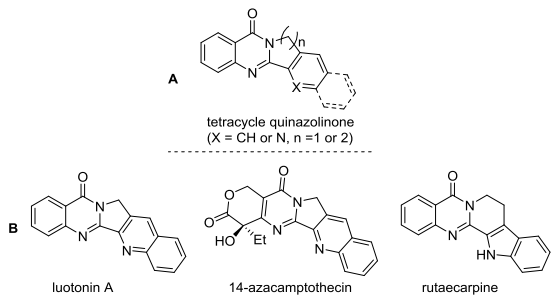
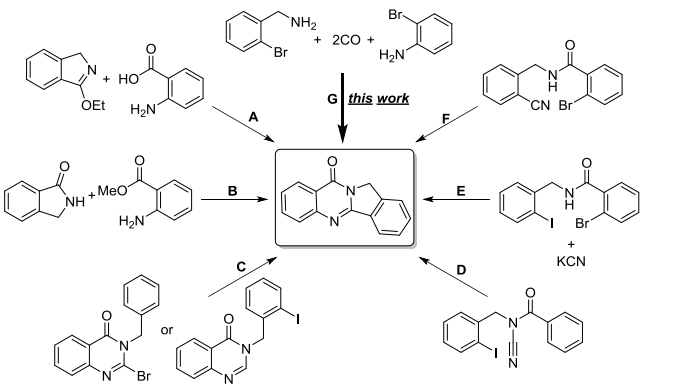


Figure 1. Selected examples of biologically active tetracycle quinazolines.

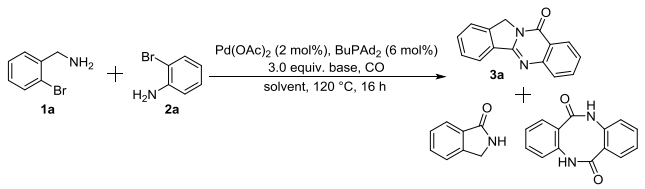


Scheme 1. Reaction pathways to construct tetracycle quinazolinone.

Since the discovery of palladium-catalyzed carbonylation by Heck and co-workers in 1974,[9] this methodology has become a versatile tool to implant C_1-unit from carbon monoxide (CO), one of the cheapest C_1 sources, into various parent molecules.[10] Particularly in the preparation of heterocyclic compounds, palladium-catalyzed carbonylation exhibits the characters of wide substrates scope and high

efficiency.[11] Based on these merits and our consistent research interests on searching new synthetic methods for 4(3*H*)-quinazolinone and its analogs,[12] we intended to realize the highly-efficient construction of tetracycle quinazolinone through the palladium-catalyzed carbonylation of commercially available 2-bromobenzylamine and 2-bromoaniline as the starting materials (Scheme 1, pathway **G**).

Table 1. Palladium-catalyzed carbonylative synthesis of isoindolo[1,2-*b*]quinazolin-10(12*H*)-one: Optimization.[a]

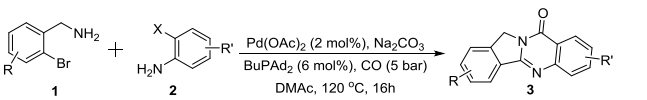


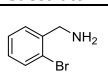
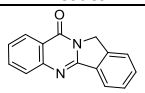
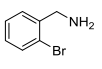
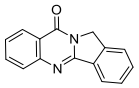
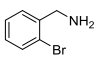
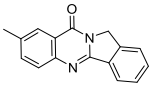
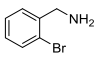
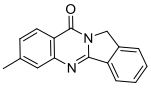
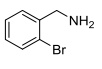
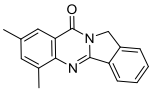
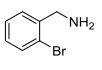
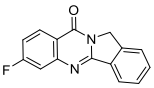
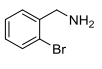
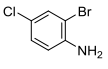
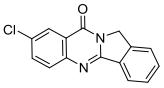
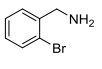
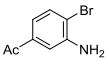
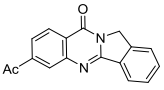
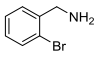
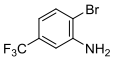
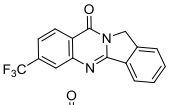
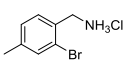
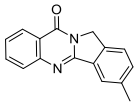
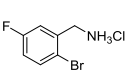
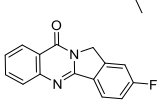
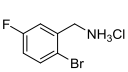
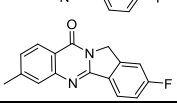
Entry	Base	CO (bar)	Solvent	Yield[b]
1	K_2CO_3	10	DMAc	11%
2	Na_2CO_3	10	DMAc	69% (66%)
3	Cs_2CO_3	10	DMAc	0%
4	K_3PO_4	10	DMAc	28%
5	Na_2CO_3	10	DMF	41%
6	Na_2CO_3	10	Toluene	0%
7	Na_2CO_3	10	1,4-Dioxane	16%
8	Na_2CO_3	10	DMSO	21%
9	Na_2CO_3	10	DMAc	72%[c]
10	Na_2CO_3	10	DMAc	57%[c,d]
11	Na_2CO_3	10	DMAc	72%[c,e]
12	Na_2CO_3	10	DMAc	51%[c,f]
13	Na_2CO_3	10	DMAc	82% (79%)[c,g]
14	Na_2CO_3	5	DMAc	80% (78%)[c,g]
15	Na_2CO_3	2	DMAc	77%[c,g]

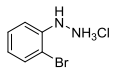
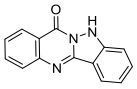
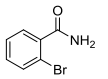
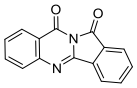
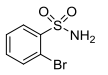
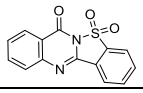
[a]Unless otherwise stated, the reaction was conducted on a 0.50 mmol scale (0.50 mmol of **1a**, 0.5 mmol of **2a**, 1.5 mmol base and 2 mL solvent). Reaction time was 16h. Ad = adamantyl; DMAc = *N*,*N*-dimethylacetamide; DMF = *N*,*N*-dimethylformamide; DMSO = dimethyl sulfoxide. [b]GC yields with *n*-hexadecane as an internal standard, isolated yields in parentheses. [c]5.0 equiv. Na_2CO_3 instead of 3.0 equiv. Na_2CO_3. [d]1mol% $Pd(OAc)_2$ and 3 mol% $BuPAd_2$. [e]Reaction time was prolonged to 32 h. [f]4.0 mL DMAc instead of 2.0 mL DMAc. [g]0.50 mmol of **1a**, 0.60 mmol of **2a**.

Initially, we choose 2-bromobenzyl amine and 2-bromoaniline as the substrates, $Pd(OAc)_2$ (2 mol%) and $BuPAd_2$ (6 mol%) as the catalyst system, under 10 bar of CO in DMAc to test the influences of bases (Table 1, entries 1-4). To our delight, 66% of isoindolo[1,2-*b*]quinazolin-10(12*H*)-one can be isolated with Na_2CO_3 as the base while the other bases gave low or no yield (Table 1, entry 2). The yield of the desired product cannot be further improved by solvents variation (Table 1, entries 5-8). Then phosphine ligands testing were carried out subsequently, PPh_3 (0%), PCy_3 (32%), Xantphos (17%) and DPPP (53%) as alternative and commonly applied ligands all resulted decreased yields compared with $BuPAd_2$ (Table 1, entry 2). At this stage, variation of the loadings of base and catalyst and pressure of CO were performed. We found that decreasing the loading of base or prolong reaction time have positive effective on the result (Table 1, entries 9 and 11); while negative effects were observed from lowered catalyst loading or diluted reaction media (Table 1, entries 10 and 12). Finally, 79% of isolated yield of the desired product can be achieved by using 1.2 equivalent of 2-bromoaniline (Table 1, entry 13). Interestingly, good yield of the quinazolinone can be prepared even under 2 bar of carbon monoxide (Table 1, entry 15). In the optimization process, dibenzo[*b*,*f*][1,5]diazocine-6,12(5*H*,11*H*)-dione and isoindolin-1-one as the by-products from carbonylative dimerization of 2-bromoaniline and intramolecular carbonylation of 2-bromobenzyl amine could be detected by GC-MS.

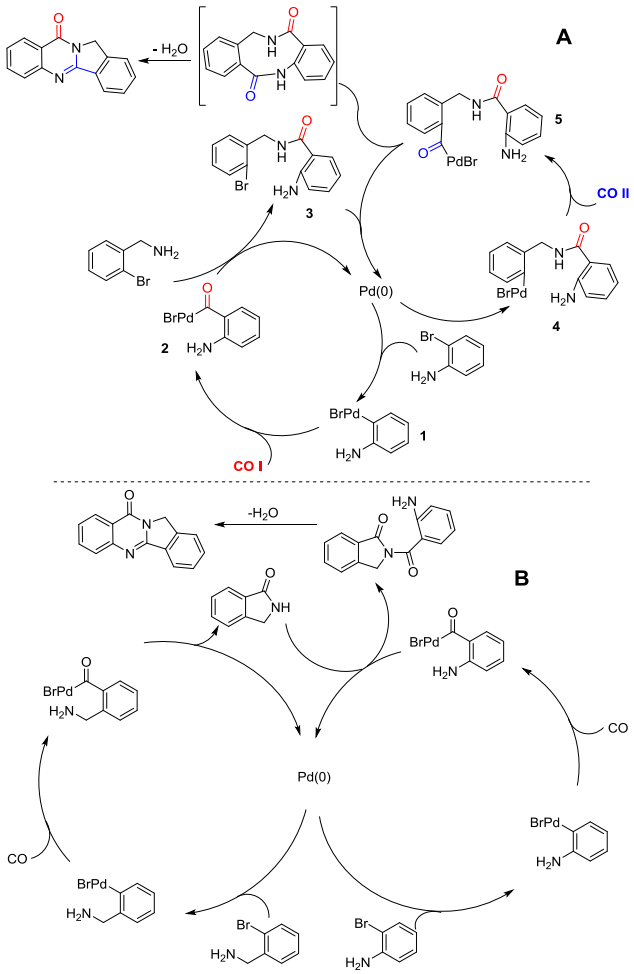
Table 2. Palladium-catalyzed carbonylative synthesis of isoindolo[1,2-*b*]quinazolin-10(12*H*)-ones: Substrates testing.[a]



Entry	Substrate 1	Substrate 2	Product	Yield[b]
1				78%
2				82%
3				78%
4				81%
5				69%
6				72%
7				84%
8				70%
9				27%
10				76%[c]
11				73%[c]
12				70%[c]

13				0%
14				0%
15				0%

[a] The reaction was conducted on a 0.50 mmol scale (0.50 mmol of **1**, 0.6 mmol of **2**), Na_2CO_3 (1.5 mmol; 3 equiv.), DMAc (2 mL), CO (5 bar), 120°C, 16h. [b] Isolated yields. [c] 4.0 equiv. Na_2CO_3 was used.



Scheme 2. Proposed reaction mechanisms.

With the best reaction conditions in hand, we are interested to see the generality and limitation of this procedure (Table 2). In general, good yields of the desired tetracycle quinazolinones were isolated from the corresponding starting materials. Regarding the functional group tolerance, not only methyl at various positions but also fluoro and chloro can be tolerated (Table 2, entries 3-7). Strong electron-withdrawing group such as acetyl and trifluoromethyl can lead the substrate highly activated and become challenge in palladium-catalyzed carbonylative coupling reactions. In this system, activated bromides can be applied as substrates without further optimization and gave the desired trtracycle quinazolinones in moderate to good yields (Table 2, entries 8 and 9). However, 2-bromopyridin-3-amine failed to give the corresponding product with 2-bromobenzylamine. Then different 2-bromobenzylamines were tested, and both methyl and fluoro substituents are tolerable under the system (Table 2, entries 10-12). Here, the ammonium salts were applied instead of the free benzyl amine, which have advantages include more stable and easy storage. Unfortunately, (2-bromophenyl)hydrazine, 2-bromobenzamide and 2-bromobenzenesulfonamide as analogues of 2-bromobenzylamine did not provide any of the desired products (Table 2, entries 13-15).

Based on these results and literature, possible reaction pathways have been proposed. As shown in Scheme 2 A, the reaction starts with the oxidative addition of Pd(0) to 2-bromoaniline and give complex **1**. The acylpappladium complex **2** can be produced after the coordination and insertion of CO, which will react with 2-bromobenzyl amine to provide a stable intermediate **3**. Then the in situ produced intermediate **3** will participate in another catalytic cycle with Pd(0). The intermediate 11,12-dihydro-5*H*-dibenzo[*b*,*g*][1,5]diazonine-6,13-dione will be formed after inserted the second molecular of CO. Finally, the more basic benzylic amine attacks the carbonyl and eliminates the final product. However, as the observation of isoindolin-1-one in optimization process, we think Mechanism B is possible as well.

Conclusions

In conclusion, an interesting and effective procedure for the synthesis of isoindolo[1,2-*b*]quinazolin-10(12*H*)-ones has been developed. Under the assistant of palladium catalyst with 2-bromoanilines and 2-bromobenzyl amines as commercially available substrates, the desired products were isolated in good yields by incorporating two molecules of CO.

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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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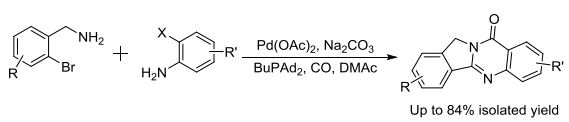

Up to 84% isolated yield

An interesting palladium-catalyzed carbonylative procedure for the synthesis of isoindolo[1,2-*b*]quinazolin-10(12*H*)-ones from commercially available 2-bromoanilines and 2-bromobenzyl amines has been developed. The desired products were isolated in good yields.