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Heterocycles

A Novel Domino Synthesis of Quinazolinediones by Palladium-Catalyzed Double Carbonylation

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Abstract: Combining commercially available bromoanilines and bromobenzonitriles in a novel double carbonylation process allows for a straightforward synthesis of isoindolo[1,2-b]quinazoline-10,12-diones. At least five different C–C and/or C–N bonds are selectively formed in this 3-component reaction, which likely proceeds through sequential carbonylation–cyclization–isomerisation–carbonylation steps. Notably, two molecules of CO are inserted in this highly efficient palladium-catalyzed process.

The efficient synthesis of heterocycles represents one of the most important targets for organic synthesis, because of their broad applications in pharmaceuticals, agrochemicals, and special materials.[1] Notably, seven out of the top ten pharmaceutical products by worldwide sales in 2009 are heterocyclic compounds.[2] Among the multitude of heterocycles known, quinazolinediones have an interesting fused nitrogen-containing organic framework.[3] Their derivatives display attractive biological activities, including anorexic as well as antihypertensive effects, and several drugs with related structures are applied in therapy.[4] Due to this importance, a number of procedures for the synthesis of quinazolinediones have been developed in the past decades.[5] In general, these protocols are based on the reaction of anthranilamide with phthalic anhydride or the reductive coupling of N-substituted 2-nitrobenzamides and 2-formylbenzoic acids. Although efficient, several substitution patterns cannot be easily accessed from these substrates. Thus, multi-step procedures are also used.

Domino reactions, in which the subsequent reaction step is a consequence of the functional group formed in the previous step, have become a key tool for improving the efficiency of organic synthesis. Advantageously, domino processes often allow for improved atom economy and circumvent isolating several intermediates and thus avoid waste generation.[6] Interestingly, the integration of modern palladium-catalyzed coupling reactions into domino processes enables the creation of significantly increased structural diversity from easily available building blocks. In this respect, carbonylative coupling reactions allow for the construction of a variety of carbonyl-containing compounds, as well as a number of important heterocycles.[7] Notably, CO is one of the cheapest C1 feedstocks available. While the advantages of incorporating one CO molecule are well-demonstrated, the incorporation of two CO molecules into the parent structure in a one-pot manner is even more appealing but still challenging.[8]

Based on our continuing interest in the carbonylative synthesis of heterocycles,[9] herein we wish to report a novel reaction cascade to give isoindolo[1,2-*b*]quinazoline-10,12-dione (**3**) through a palladium-catalyzed double-carbonylation process. Starting from commercially available substrates, at least five bonds were efficiently created during the reaction in a one-pot process, and two CO molecules were incorporated.

Initially, we investigated the palladium-catalyzed carbonylation of 2-bromobenzonitrile **1a** and 2-bromobenzamide **2a**. To our surprise, the fused heterocyclic product **3a** was formed containing an isoindolinone and also a quinazolinone ring. Later on, NMR spectroscopic assignments of the product structure were confirmed by the crystal structure of **3ad** (Figure 1).

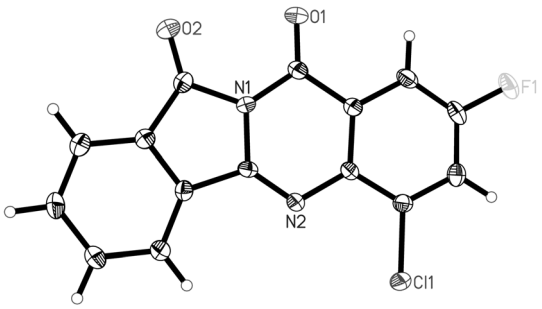

Figure 1. X-ray structure of compound **3ad**. Displacement ellipsoids are drawn at the 50% probability level. Only one of the two molecules of the asymmetric unit is shown.

In order to optimize the reaction conditions, various phosphine ligands were tested in the presence of 2 mol% of $Pd(OAc)_2$ as catalyst precursor. In general, trialkylphosphines such as $BuPAd_2$, and PCy_3 gave better yields compared to PPh_3, DPPF (1,1′-bis(diphenylphosphino)ferrocene), and DPPP (1,3-bis(diphenylphosphino)propane). Finally, $PtBu_3{\cdot}HBF_4$ was found to be the most suitable ligand for this reaction. After further testing of the effect of different solvents (DMF, 1,4-dioxane, and toluene) and bases (K_2CO_3, DiPEA, DBU, and Et_3N), toluene

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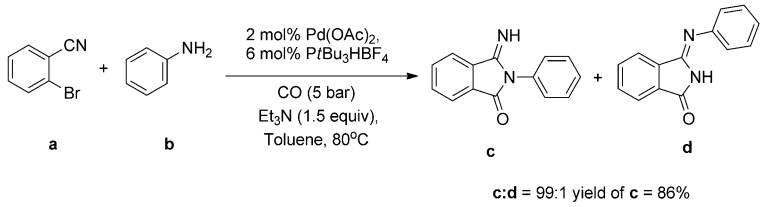
as the reaction media and Et_3N as the base was found to be the most suitable combination. Hence, we succeeded in obtaining **3aa** in 83% isolated yield under our optimized conditions (**1** (1 equiv), **2** (1.05 equiv), 2 mol% $Pd(OAc)_2$, 6 mol% $PtBu_3{\cdot}HBF_4$, 3 equiv of Et_3N, toluene, 100 °C, 5 bar of CO).

To reveal the reaction pathway, aniline was reacted under similar conditions with 2-bromobenzonitrile under a carbon monoxide atmosphere; compound **c** was obtained as the major component and **d** was observed as well. After optimization, **c** could be obtained with 86% yield (Scheme 1, for detail, please see the Supporting Information).



Scheme 1. Reaction between 2-bromobenzonitrile and aniline.

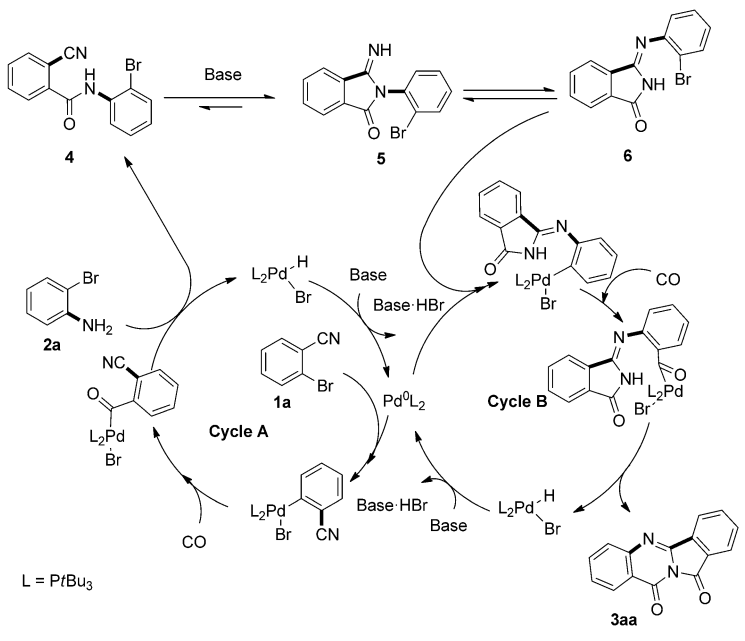
Based on the structural determination of the final product, a likely reaction pathway is given in Scheme 2. Starting from 2-bromoaniline **2a** and 2-bromobenzonitrile **1a**, the first aminocarbonylation occurred forming amide **4** (cycle A). It should be noted that the oxidative insertion of the active palladium species occurrs preferentially at **1a** due to the higher reactivity. Next, base-catalyzed isomerization–cyclization should form the iminoisoindolinone **5**.[10] Interestingly, **5** does not undergo another carbonylation reaction, instead the unexpected isomerization of **5** to **6** occurs, probably due to steric effects. Subsequent intramolecular carbonylative coupling forms **3aa** as the final product (cycle B).

Next, we investigated the generality and limitations of this methodology. Hence, without further optimization, the reaction of 2-bromobenzonitrile with nine different bromoanilines **2b**–**2j** was tested. When **2b** was used, the chloro substituent was found to stay intact under these conditions, and a good yield (70%) of **3ab** was obtained (Table 1, entry 2). Anilines with electron-withdrawing substituents gave the desired products (**2c**, **2d**, and **2f**) in 57–63% yield. Gratifyingly, when **2e** was subjected to the reaction conditions, the acetyl group was found to be well-tolerated, leading to **3ae** in 87% isolated yield! Similarly, 82% of the desired product was produced by using the corresponding cyano-substituted 2-bromoaniline as a substrate (Table 1, entry 7). Furthermore, the methyl-substitued 2-bromoanilines (**2h** and **2i**), worked quite well, and the corresponding quinazolinediones were obtained in 73 and 61% yield, respectively. Considering the broad applications of the trifluoromethyl group in bioactive compounds, **2j** was tested as well. However, in this latter case only 37% of the corresponding product **3aj** was obtained. Despite the lower yield, isolation of **3aj** was easy. More specifically, the purification of all the products was facile and no column chromatography was necessary. The pure compounds were obtained by simply recrystallizing the crude reaction mixture from ethanol. This simple isolation certainly adds to the value of the synthetic methodology.

To further demonstrate the applicability of our procedure, we then performed coupling reactions of 2-bromoaniline with ten different 2-bromobenzonitriles **1b**–**1i**.

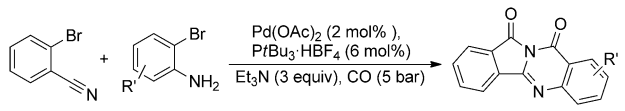
As shown in Table 2, no obvious steric effects on the 2-bromobenzonitrile ring were observed. Thus, good yields (75–87%) of the respective quinazolinediones were obtained with either 3-, 4- or 5-methyl-substituted 2-bromobenzonitriles as substrates (Table 2, entries 1–3). Also, a similar yield was obtained by using 5-methoxy-2-bromobenzonitrile as the starting material (88%; Table 2, entry 4). 63–76% of the desired prodcuts were successfully isolated using 4- and 6-fluoro-substitued 2-bromobenzonitriles **1f** and **1g**. When changing the bromo substituent to a iodo leaving group, the reaction proceeded slightly better (72% isolated yield), and the identical product was obtained. Finally, satisfactory results were achieved in the carbonylative coupling of **1b** with **2h**, **2g**, and **2e** without any further optimization (82, 79, and 84%, respectively).

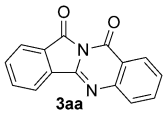
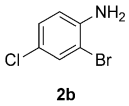
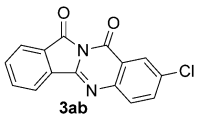
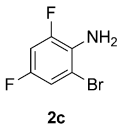
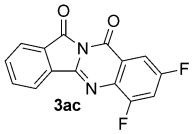
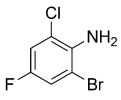
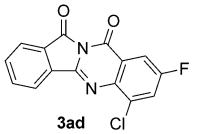
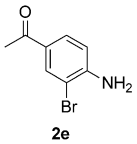
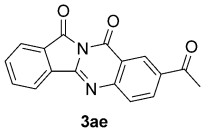
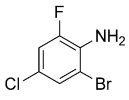
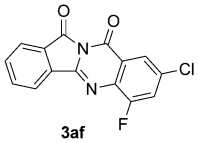
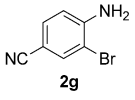
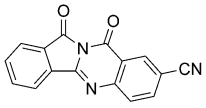
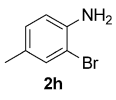
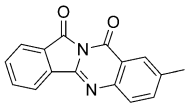
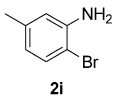
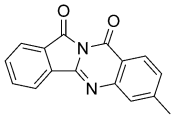
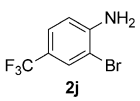
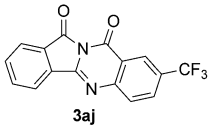
Comparing the NMR spectra of the different products, the similar heterocyclic core is unambiguously proven. For example, in the ^{13}C NMR spectrum of **3ga**, the fluorine atom has a smaller coupling constant with the carbonyl carbon ($^4J_{C-F} = 2.6$ Hz) compared to the imidamido carbon ($^3J_{C-F} = 4.8$ Hz), which also matches the 2D-NMR analysis of compound **3ca**, in which the methyl substituent that is originally at the *ortho*-position to the bromo substituent ends up in the *ortho*-position of the amido carbon on the isoindolinone ring.



Scheme 2. Proposed reaction mechanism.

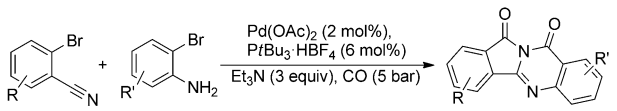
Table 1. Pd-catalyzed carbonylative synthesis of quinazolinediones from different 2-bromoaniline derivatives and 2-bromobenzonitrile.[a]

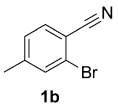
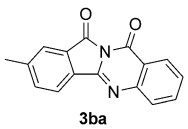
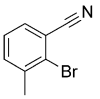
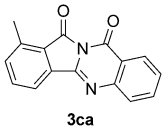
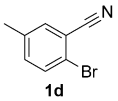
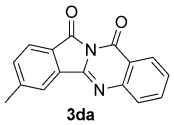
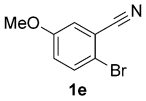
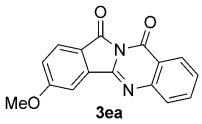
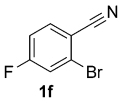
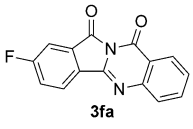
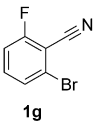
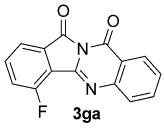
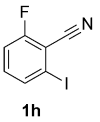
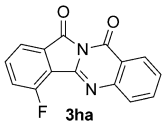
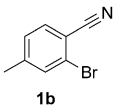
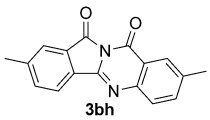
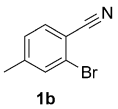
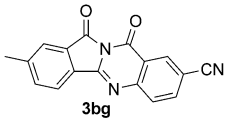


Entry	2-Bromoanilines	Product	Yield [%][b]
1	 **2a**	 **3aa**	83
2	 **2b**	 **3ab**	70
3	 **2c**	 **3ac**	63
4	 **2d**	 **3ad**	57
5	 **2e**	 **3ae**	87
6	 **2f**	 **3af**	60
7	 **2g**	 **3ag**	82
8	 **2h**	 **3ah**	73
9	 **2i**	 **3ai**	61
10	 **2j**	 **3aj**	37

[a] 2-Bromobenzonitrile (1 mmol), 2-bromoaniline (1.1 mmol), CO (5 bar), $Pd(OAc)_2$ (2 mol%), $PtBu_3{\cdot}HBF_4$ (6 mol%), toluene (4 mL), Et_3N (3 mmol), 100 °C, 20 h. [b] Isolated yields.

Table 2. Pd-catalyzed carbonylative synthesis of quinazolinediones from 2-bromoanilines and different 2-bromobenzonitriles.[a]



Entry	2-Bromoanilines	Product	Yield [%][b]
1	 **1b**	 **3ba**	78
2	 **1c**	 **3ca**	75
3	 **1d**	 **3da**	87
4	 **1e**	 **3ea**	88
5	 **1f**	 **3fa**	76
6	 **1g**	 **3ga**	63
7	 **1h**	 **3ha**	72
8[c]	 **1b**	 **3bh**	82
9[d]	 **1b**	 **3bg**	79
10[e]	**1b**	**3be**	84

[a] 2-Bromobenzonitrile derivatives (1 mmol), 2-bromoaniline (**2a**) (1.1 mmol), CO (5 bar), $Pd(OAc)_2$ (2 mol%), $PtBu_3{\cdot}HBF_4$ (6 mol%), toluene (4 mL), Et_3N (3 mmol), 100 °C, 20 h. [b] Isolated yields. [c] **2h** instead of **2a**. [d] **2g** instead of **2a**. [e] **2e** instead of **2a**.

In summary, the first palladium-catalyzed double-carbonylation process for the synthesis of quinazolinediones has been developed. Starting from commercially available 2-bromobenzonitriles and 2-bromoanilines a series of isoindolo[1,2-b]quinazoline-10,12-diones was synthesized in a straightforward manner with good isolated yields (around 20 examples). Notably, in this novel domino process, both inter- and intramolecular carbonylation reactions take place, and two CO molecules are incorporated in the parent product structure. Considering that at least 5 different C–C and C–N bonds are formed, each of the individual reaction steps proceeds with high selectivity and excellent yield. Further applications of this methodology are currently underway in our laboratory.

Experimental Section

General procedure for the synthesis of compound 3

An oven-dried 12 mL vial with stir bar was charged with 2-bromobenzonitrile (1.0 mmol, 1 equiv), 2-bromoaniline (1.1 mmol, 1.1 equiv), $Pd(OAc)_2$ (0.02 mmol, 2 mol%), and $PtBu_3{\cdot}HBF_4$ (0.06 mmol, 6 mol%) and was put into a 25 mL Schlenk and then evacuated and refilled with argon three times. Then, toluene (3 mL), Et_3N (3 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 5 bar CO was adjusted at ambient temperature. The reaction mixture was heated overnight (20 h) at 100 °C. After the reaction finished, the autoclave was cooled down to room temperature and the pressure was released carefully. The crude reaction mixture was transferred into a 50 mL beaker with 20 mL of water. After vigorous stirring for 1 min, the crude product was obtained, filtered and washed with 10 mL of 5:1 pentane/EtOAc, and dried under vacuum. Pure compound was obtained after recrystallization in EtOH. For some of the compounds, that is, those of low solubility, pure compound could also be obtained by combining the crude product and ethanol and heating to the boiling point of ethanol, followed by cooling down and filtration.

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Keywords: carbonylation · coupling · domino reactions · multicomponent reactions · palladium

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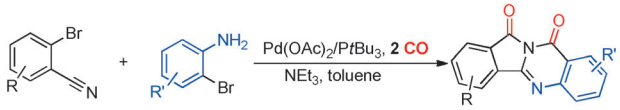

InCOrporation: A palladium-catalyzed domino synthesis of diverse quinazolinediones in an efficient double-carbonylation mode has been developed (see scheme).

Heterocycles

H. Li, W. Li, A. Spannenberg, W. Baumann, H. Neumann, M. Beller, X.-F. Wu**

■■ – ■■

A Novel Domino Synthesis of Quinazolinediones by Palladium-Catalyzed Double Carbonylation