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Palladium-Catalyzed Synthesis of Isoindoloquinazolinones *via* Dicarbonylation of 1,2-Dibromoarenes

Cite this: DOI: 10.1039/xoxxoooooox

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Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

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Abstract. A convenient procedure for the carbonylative synthesis of isoindoloquinazoolinones has been developed. By using 1,2-dibromobenzenes and 2-aminobenzyl amine as substrates and palladium as the catalyst, the desired products were isolated in moderate to good yields with the installation of two molecules of carbon monoxide. Notably, this is the first example on carbonylative synthesis of batracylin analogues.

Isoindoloquinazolinones represent as the core structure in many biologically active molecules.[1] Among the known isoindoloquinazolinones, batracylin (Figure 1) is a representative example, which has been reported to be an anticancer agent and currently undergoing clinical evaluation as an anticancer agent at the National Cancer Institute.[2] Some similar structures, such as (-)-vasicine, lutonins and tryptanthrin, have been reported with anti-inflammatory and antitumoural activities as well.[3] Owning to their pharmacological interest, various procedures have been developed for their preparation.[4] However, most of the known procedures require already quite complexed compounds, such as phthalic anhydrides or phthalimides, as their parent substrates.

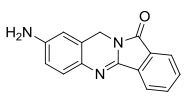
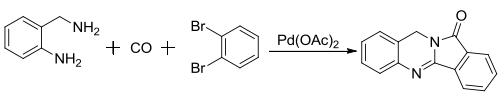


Figure 1. Structure of batracylin.

Palladium-catalyzed carbonylation reactions have already become a true tool box in modern organic synthesis, which offer promising options for the preparation of carbonyl containing compounds. By incorporating one or even more molecules of CO into the parent structure, the carbon chain can be easily increased and the resulted products are ready for further modification which hold their own importance as well.[5] As the mentioned advantages of carbonylation reactions, it is even more attractive to apply carbonylations in the synthesis of biological active heterocyclic compounds.[6] Here, we wish to report our results on carbonylative synthesis of isoindoloquinazolinone derivatives. By using 1,2-dibromobenzenes and 2-aminobenzyl amine as readily available substrates, the desired products were isolated in good yields by incorporation of two molecules of CO. Remarkably, this is the first example on carbonylative synthesis of isoindoloquinazolinones. As the products belong to the analogue of batracylin, we believe our procedure can enrich the family of isoindoloquinazolinones and help exploring the biological applications of batracylin derivatives.

Initially, the experiment was performed with NEt_3 as base, DMF as solvent, with $Pd(OAc)_2$/$BuPAd_2$ as the catalyst system under 10 bar of CO. The desired product was formed in 41% yield by using 2-aminobenzyl amine (0.5 mmol) and 1,2-dibromobenzene (0.5 mmol) as substrates (Table 1, entry 1). Then we tested three other bases, which did not give better yield (Table 1, entries 2-4). The influence of the nature of the solvent was also checked. An 80% yield of isoindolo[1,2-*b*]quinazolin-12(10*H*)-one was isolated by using DMAc as the solvent (Table 1, entry 5). At lower temperature or CO pressure, the yield of the target product decreased (Table 1, entries 7 and 8). Additionally, several phosphine ligands were tested in DMAc with NEt_3 as base (Table 1, entries 9-13). In general, good yields could be observed, but $BuPAd_2$ was proved to be the best ligand for this transformation.

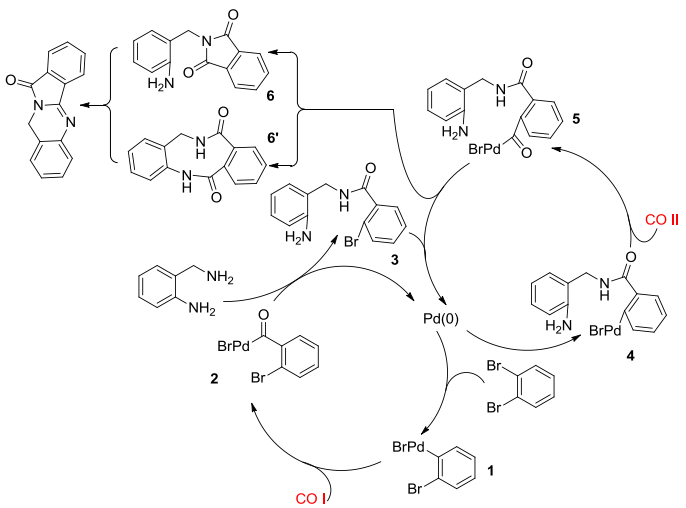
Table 1. Palladium-Catalyzed Carbonylative Synthesis of Isoindoloquinazolinone: Optimization.[a]



Entry	Ligand	Base	Solvent	Yield[b]
1	$BuPAd_2$	NEt_3	DMF	41%
2	$BuPAd_2$	DBU	DMF	38%
3	$BuPAd_2$	K_2CO_3	DMF	33%
4	$BuPAd_2$	K_3PO_4	DMF	12%
5	$BuPAd_2$	NEt_3	DMAc	88% 80%[c]
6	$BuPAd_2$	NEt_3	Dioxane	31%
7	$BuPAd_2$	NEt_3	DMAc	51%[d]
8	$BuPAd_2$	NEt_3	DMAc	39%[e]
9	PPh_3	NEt_3	DMAc	16%
10	DPEphos	NEt_3	DMAc	61%
11	Xantphos	NEt_3	DMAc	60%
12	DPPP	NEt_3	DMAc	60%
13	BINAP	NEt_3	DMAc	75%

[a] 1,2-Dibromobenzene (1 mmol), 2-aminobenzyl amine (1 mmol), $Pd(OAc)_2$ (2 mol%), ligand (6 mol%), base (3 equiv.), solvent (2 mL), CO (10 bar), 120 °C, 16h. [b] Yields were determined by GC using hexadecane as internal standard, calculated based on 1,2-dibromobenzene. [c] Isolated yield. [d] CO (2 bar). [e] 100 °C.

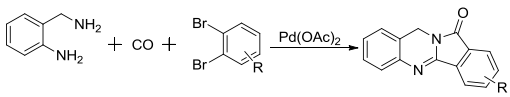
Regarding the reaction mechanism, a possible reaction pathway has been proposed and shown in Scheme 1. The reaction started with Pd(0) which undergoes oxidative addition with 1,2-dibromobenzene to give organopalladium species **1**. Subsequently, followed by the coordination and insertion of CO to give acylpalladium complex **2** and then provided the intermediate **3** after nucleophilic attack by 2-aminobenzyl amine. *N*-(2-Aminobenzyl)-2-bromobenzamide will undergoes oxidative addition again with Pd(0) and then installation of CO to provide intermediate **5**. 12,13-Dihydro-5*H*-dibenzo[*b*,*g*][1,5]diazonine-6,11-dione **6'** and 2-(2-aminobenzyl)isoindoline-1,3-dione **6** are the two possible intermediate which both will give the targeted isoindolo[1,2-*b*]quinazolin-12(10*H*)-one after intramolecular condensation.

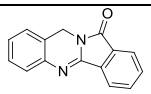
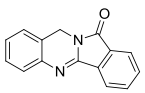
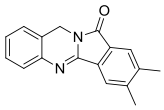
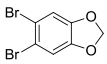
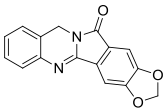
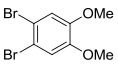
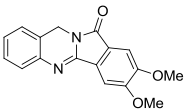
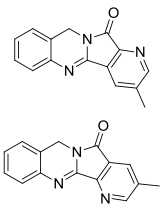
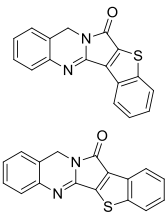
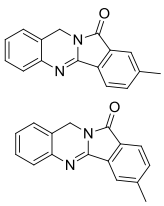
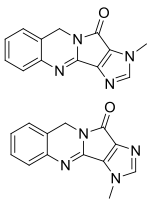
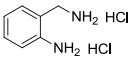
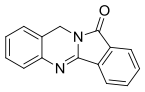


Scheme 1. Proposed Reaction Mechanism.

With the best reaction conditions in hand (Table 1, entry 5), the substrates testing were carried out subsequently. As shown in Table 2, several kinds of isoindoloquinazolinones were produced and isolated in moderate to good yields. 84% isolated yield was achieved by using 1,2-dibromo-4,5-dimethoxybenzene as substrate (Table 2, entry 5). Moderate yields of the desired products were isolated when similar electron property substrates were applied (Table 2, entries 3,4,8). Since, no significant amount of by-product was detected in GC and GC-MS analysis; we think the difference in solubility may response for the yields variation. For the activated substrates, dehalogenation products are the main by-product. In the case of substituted 1,2-dibromoarenes, two isomers were formed in different ratio.

Table 2. Palladium-Catalyzed Carbonylative Synthesis of Isoindoloquinazolinones: Scope.[a]



Entry	1,2-Dihaloarene	Product	Yield[b]
1			80%
2			78%
3			56%
4			47%
5			84%
6			78% (1.3:1)
7			48% (2.3:1)
8			36% (1:1)
9			<10[c]
10			50%[d]

[a] 1,2-Dibromobenzenes (0.5 mmol), 2-aminobenzyl amine (0.5 mmol), $Pd(OAc)_2$ (2 mol%), $BuPAd_2$ (6 mol%), NEt_3 (3 equiv.), DMAc (2 mL), CO (10 bar), 120 °C, 16h. [b] Isolated yield. [c] Determined by GC-MS [d] NEt_3 (5.0 equiv.)

In conclusion, an interesting and convenient procedure for the carbonylative synthesis of isoindoloquinazoolinones has been developed. In the presence of palladium catalyst with 1,2-dibromobenzenes and 2-aminobenzyl amine as substrates, the desired products were isolated in moderate to good yields with the installation of two molecules of carbon monoxide. Notably, this is the first example on carbonylative synthesis of isoindoloquinazoolinones.

General information

Reactions were run under an argon atmosphere with exclusion of moisture from reagents and autoclaves. All substrates were purchased from Sigma–Aldrich and were used as received. Solvents were dried from molecular sieves and kept under argon. NMR spectra were recorded on the Bruker AV 300 spectrometers. All chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) in Hz. All chemical shifts are reported relative to tetramethylsilane (δ 0.0 for ^{1}H NMR in DMSO-d_6, $CDCl_3$) and *d*-solvent peaks (δ 77.00 for ^{13}C NMR, chloroform and for DMSO-d_6, δ 39.50), respectively. All measurements were carried out at room temperature unless otherwise stated. Mass spectra were recorded on an AMD 402/3 or a HP 5989A mass selective detector. Gas chromatographic analysis was performed on an Agilent HP-5890 instrument with an FID detector and an HP-5 capillary column (poly(dimethylsiloxane) with 5% phenyl groups, 30 m, 0.32 mm i.d., 0.25 mm film thickness) with argon as the carrier gas.

Experimental section

The reaction was carried out in a Parr Instruments 4560 series 300 mL autoclave containing an alloy plate with wells for five 12 mL Wheaton vials. $Pd(OAc)_2$, (2.0 mol%), *CataC*Xium A (6.0 mol%; $BuPAd_2$), and a magnetic stir bar were placed in each vials, which were then capped with a septum equipped with an inlet needle and flushed with argon. Then NEt_3 (3 mmol, 3.0 equiv.), *o*-dibromobenzene (0.5 mmol), 2-aminobenzyl amine (0.5 mmol) and DMAc (2 mL) were added to the vial *via* syringe. The vials were placed in an autoclave, which was then purged several times with argon. Subsequently it was filled with 10 bars of CO at room temperature and heated at 120 °C for 16 h. After the reaction, the autoclave was cooled to room temperature and vented to discharge N_2. 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 occurred by flash chromatography on silica gel.

Acknowledgements:
We thank the state of Mecklenburg-Vorpommern and the Bundesministerium für Bildung und Forschung (BMBF) for financial support. We also thank Dr. W. Baumann, Dr. C. Fischer, and S. Buchholz (LIKAT) for analytical support.

Notes and references:

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Electronic Supplementary Information (ESI) available: [analytic data and general procedure]. See DOI: 10.1039/c000000x/

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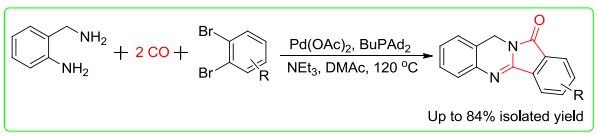

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