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Carbonylation

# Carbonylation of Anthranilic Acid with Aryl and Heteroaryl Bromides to Synthesize Benzoxazinone Derivatives

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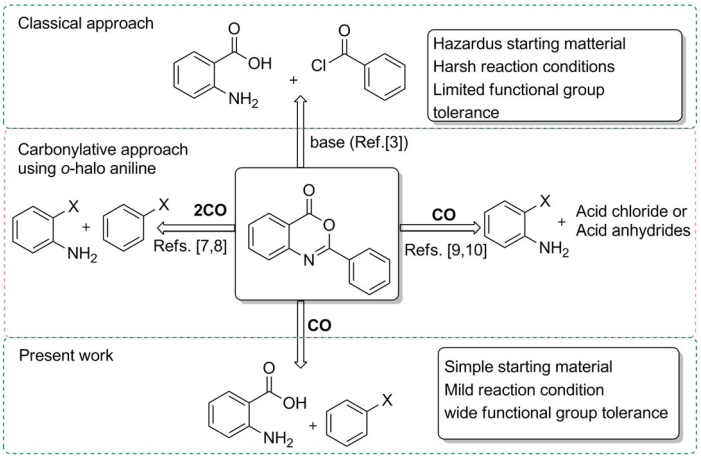
**Abstract:** A simple and efficient, $PdCl_2(PhCN)_2$/$P(tBu)_3$·$HBF_4$-catalyzed carbonylative cyclization of anthranilic acid with aryl bromide was investigated for the synthesis of benzoxazinones under mild reaction conditions. The developed protocol has been extended for the synthesis of quinazolin-4(3*H*)-ones. Furthermore, the tolerance of a wide range of functional groups on anthranilic acid as well as on aryl bromide demonstrates the practical utility of the protocol.

Benzoxazinone motifs are the key backbone of numerous biological active molecules and make a prevalent impact on the field of medicinal chemistry.[1] In addition, the substituted benzoxazinone derivatives have found important applications in the preparation of analgesics, anti-thrombotic, anti-inflammatory, anti-fungal, and antibacterial agents.[2] The classical methods for the synthesis of benzoxazinones involves the condensation of anthranilic acid with acid chlorides or acid anhydrides. However, the use of hazardous chemicals, harsh reaction conditions, and limited functional group tolerance confines its synthetic utility.[3]

The transition metal catalyzed carbonylation reaction gives an endless contribution in the field of synthetic organic chemistry.[4] Direct use of carbon monoxide gas as an inexpensive and easily available C1 building block is one of the most proficient processes to synthesize carbonyl compounds. Hence, several facial approaches have been well documented in literature using the palladium catalyzed carbonylation reaction to synthesize a diverse range of heterocycles.[5]

The palladium-catalyzed carbonylative synthesis of benzoxazinones via thallation and followed by carbonylation of acetanilide was initially reported by Larock and co-workers.[6] Further, the double carbonylation of 2-iodoanilines with aryl halides or triflates has been documented by Cacchi and co-workers for the synthesis of benzoxazinones.[7] Beller and co-workers have reported a similar approach to synthesize benzoxazinones using 2-bromoanilines with aryl bromides.[8] Furthermore, Alper and co-workers reported a palladium-catalyzed carbonylation of 2-iodoanilines with acid chlorides to synthesize benzoxazinones. The analogous phosphine ligand-free reaction was developed by Li and co-workers using a Pd-N-heterocyclic carbene (NHC) catalytic system.[9] In addition, Beller and co-workers developed the $K_2PdCl_4$/n-butyldiadamantylphosphine-catalyzed protocol for the synthesis of 2-alkylbenzoxazinones via a carbonylative coupling of 2-bromoanilines with symmetrical acid anhydrides.[10] In recent years, several transition metal catalyzed carbonylative C–H activation approaches have also been developed for the synthesis of benzoxazinones.[11] Considering the importance of benzoxazinones, it would be interesting to develop a simple carbonylative protocol for the synthesis of benzoxazinones using anthranilic acid as an inexpensive and easily available feedstock (Scheme 1).

In continuation with our current research interest on the development of palladium-catalyzed carbonylation reaction for the synthesis of a diverse range of carbonyl compounds,[12] herein, we wish to report a simple, efficient and novel route for the synthesis of benzoxazinone derivatives via the $PdCl_2(PhCN)_2$/$P(tBu)_3$·$HBF_4$-catalyzed carbonylation of anthranilic acid with aryl halides (Figure 1). The scope of this method




**Scheme 1.** Classical and carbonylative approach for the synthesis of benzoxazinones.

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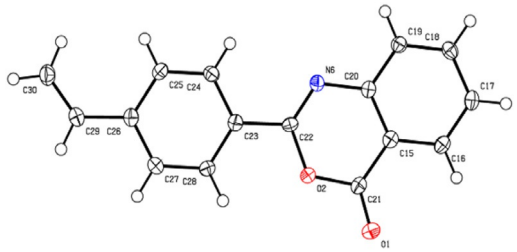
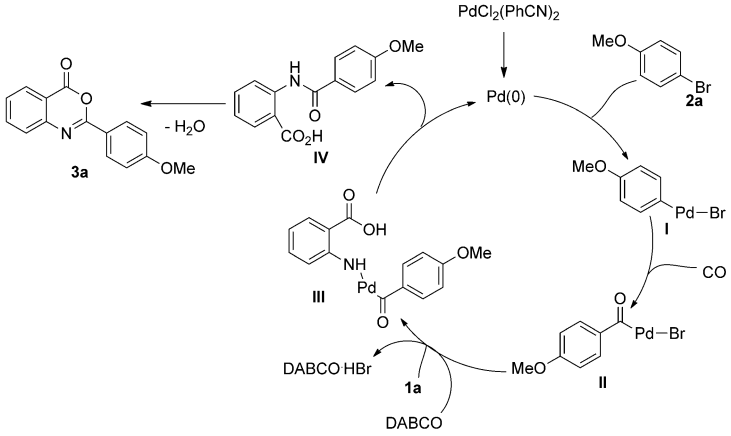


**Figure 1.** X-ray structure of compound **3o**.[16]

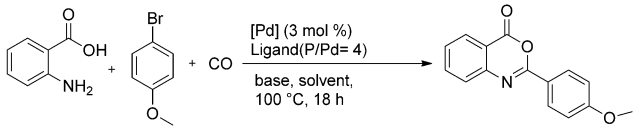
was further extended for the cascade synthesis of 2-arylquinazolinones and amino acid-derived quinazolin-4(3*H*)-ones. The present developed catalytic system shows remarkable activity and tolerates a wide variety of functional groups such as $-CH_3$, $-OCH_3$, –CN, –F, $-CO_2CH_3$, $-COCF_3$, $-NO_2$, and $-CHCH_2$.

The carbonylative cyclization reaction of anthranilic acid with 4-bromoanisole under 200 psi CO pressure was chosen as a model reaction. Initially, the model reaction was carried out using $Pd(OAc)_2$ as a catalyst and 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base in anhydrous toluene and it was observed that the desired product was formed in very poor yield (Table 1, entry 1). The properties of ligand like cone angle, bite angle and basicity play a major role in the activation of aryl bromides and aryl chlorides in cross-coupling reactions.[13] It is known that a sterically crowded, electron-rich phosphine ligand plays a significant role in the palladium-catalyzed cross-coupling reactions. Hence, we have screened a wide range of phosphine ligands. At the beginning, addition of 1,1′-bis(diphenylphosphanyl)ferrocene (dppf) led to an increase in the yield of **3a** along with formation of 4-methoxybenzoic acid in significant amount via the hydroxy carbonylation of **2a** (Table 1, entry 2). The water required for the hydroxy carbonylation might come from the condensation of **IV** (Scheme 2), which is formed by the aminocarbonylation of anthranilic acid with 4-bromoanisole. The use of molecular sieves helps to reduce the acid formation (hydroxy carbonylated product) and to increase the yield of the desire product to some extent (Table 1, entry 3). Subsequently, other phosphine ligands such as Xantphos, $P(tBu)_3{\cdot}HBF_4$, DevPhos, and SPhos were also screened for this reaction (Table 1, entries 4–7). Among all, $P(tBu)_3{\cdot}HBF_4$ performed as the best ligand and provided the desired product in 78% yield (Table 1, entry 5).




**Scheme 2.** Plausible reaction mechanism for the synthesis of benzoxazinones.

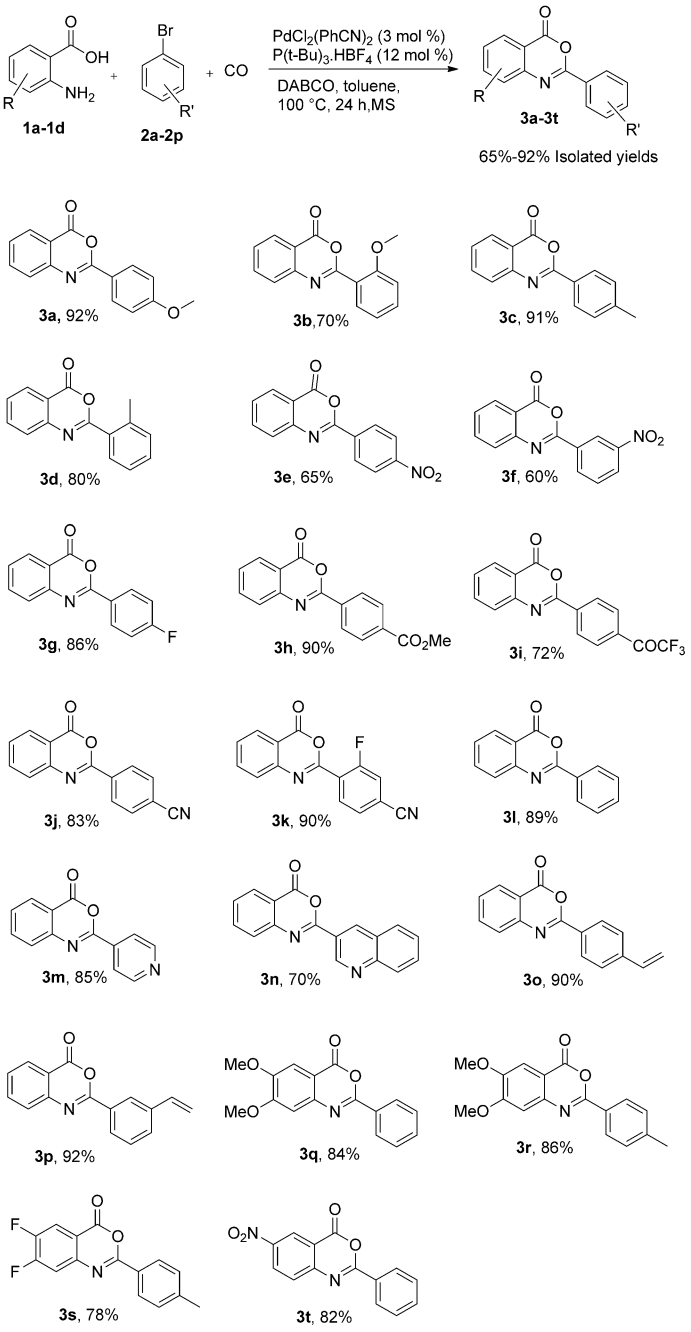
**Table 1.** Screening of reaction conditions.[a]




| Entry | Catalyst | Ligand | Base | Yield [%][b] |
|---|---|---|---|---|
| 1[c] | $Pd(OAc)_2$ | – | DABCO | <10 |
| 2[c] | $Pd(OAc)_2$ | dppf | DABCO | 38 |
| 3 | $Pd(OAc)_2$ | dppf | DABCO | 60 |
| 4 | $Pd(OAc)_2$ | xantphos | DABCO | 70 |
| 5 | $Pd(OAc)_2$ | $P(tBu)_3{\cdot}HBF_4$ | DABCO | 78 |
| 6 | $Pd(OAc)_2$ | DevPhos | DABCO | 48 |
| 7 | $Pd(OAc)_2$ | SPhos | DABCO | 54 |
| 8 | $Pd(dba)_2$ | $P(tBu)_3{\cdot}HBF_4$ | DABCO | 73 |
| **9** | **$PdCl_2(PhCN)_2$** | **$P(tBu)_3{\cdot}HBF_4$** | **DABCO** | **94** |
| 10 | $PdCl_2(PPh_3)_2$ | $P(tBu)_3{\cdot}HBF_4$ | DABCO | 64 |
| 11 | $Pd(PPh_3)_4$ | $P(tBu)_3{\cdot}HBF_4$ | DABCO | 55 |
| 12 | $PdCl_2(PhCN)_2$ | $P(tBu)_3{\cdot}HBF_4$ | $NEt_3$ | 45 |
| 13 | $PdCl_2(PhCN)_2$ | $P(tBu)_3{\cdot}HBF_4$ | DBU | 81 |
| 14 | $PdCl_2(PhCN)_2$ | $P(tBu)_3{\cdot}HBF_4$ | NaOAc | 10 |
| 15 | $PdCl_2(PhCN)_2$ | $P(tBu)_3{\cdot}HBF_4$ | $K_2CO_3$ | 30 |
| 16 | $PdCl_2(PhCN)_2$ | $P(tBu)_3{\cdot}HBF_4$ | $Na_2HPO_4$ | 18 |

[a] Reaction conditions: **1a** (1 mmol), **2a** (1.15 mmol), catalyst (3 mol%), ligand, base (2 mmol), and molecular sieves (3 Å) in toluene (10 mL) and then the reaction mixture was stirred for 24 h at 100 °C. [b] GC yields. [c] Without molecular sieves.

Next, we screened a range of palladium precursors with $P(tBu)_3{\cdot}HBF_4$ as the ligand (Table 1, entries 8–11), among them $PdCl_2(PhCN)_2$ gave **3a** in 94% yield (Table 1, entry 9). Our previous findings reveal that the choice of base is crucial in the carbonylative cyclization reaction.[14] Hence, in the next set of experiments we investigated the role of various bases on the carbonylative cyclization of anthranilic acid with 4-bromoanisole. The organic bases such as $NEt_3$ and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and inorganic bases such as NaOAc, $K_2CO_3$, and $Na_2HPO_4$ were found to be less effective (Table 1, entries 12–16). Using these optimized reaction parameters, the scope and limitations of the developed protocol was evaluated. A variety of aryl bromides react with a range of anthranilic acid to produce the corresponding benzoxazinones in good to excellent yield (Scheme 3). The model reaction gave **3a** in 92% isolated yield. The aryl bromide bearing electron-donating substituents such as $-CH_3$ and $-OCH_3$ at the *ortho* and *para* positions provided good to excellent yield of the respective products (Scheme 3, **3a**–**3d**). Furthermore, the aryl bromide bearing electron-withdrawing groups such as $-NO_2$, –F, –CN, and $-COCF_3$ were tested under the optimized reaction conditions. It




**Scheme 3.** Table Substrate scope for the synthesis of benzoxazinones. [a] Reaction conditions: **1a–1d** (1 mmol), **2a–2p** (1.15 mmol), $PdCl_2(PhCN)_2$ (3 mol%), $P(tBu)_3{\cdot}BF_4$(12 mol%), DABCO (2 mmol), and molecular sieves (3 Å) were added in toluene (10 mL) then the reaction mixture was stirred for 24 h at 100 °C. [b] Isolated yields.

was noted that the -$NO_2$ group gave the corresponding products in lower yields (Scheme 3, **3e** and **3f**), while other electron-withdrawing substituents such as –F, –CN, and –$COCF_3$ gave the desired products in good yields (Scheme 3, **3g**–**3k**). The carbonylative cyclization of anthranilic acid with bromobenzene produces 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one (**3l**) in 96% yield. Moreover, heterocyclic aryl bromides such as 4-bromopyridine and 3-bromoisoquinoline were also found to be compatible under the present catalytic system (Scheme 3, **3m** and **3n**). In addition to this, 3-bromostyrene and 4-bromostyrene could also be converted into products **3o** and **3p**, respectively (Figure 1, CCDC 1478766). No intermolecular reaction such as Heck coupling and carbonylative Heck coupling was observed. Moreover, the scope of substituted anthranilic acids with aryl bromides was also explored to produce the corresponding benzoxazinones (**3q**–**3t**) in good to excellent yields.

The present method was further extended to synthesize 2-arylquinazolinones and amino acid-derived quinazolinones. The carbonylative cyclization reaction of anthranilic acid with bromobenzene was probed to produce the benzoxazinones. After this reaction, the corresponding amines were added to the reaction mixture and heated at 100 °C for 12 h to furnish the quinazolinones **4a** and **4b** (Scheme 4).

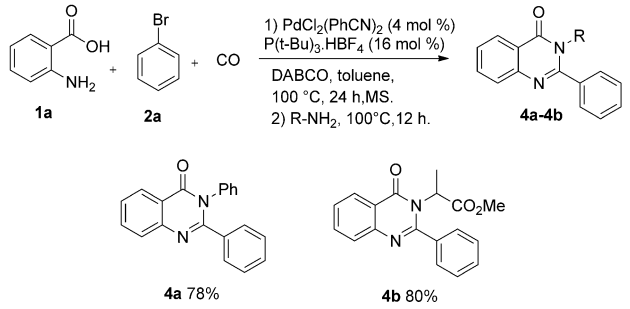
Based on the previous amino carbonylation reports,[7–9] a plausible reaction mechanism for the synthesis of benzoxizone has been illustrated (Scheme 2). At first, the oxidative insertion of in situ generated active $Pd^0$ species[15] on 4-bromoanisole **2a** produces arylpalladium intermediate **I**. Next, in the presence of carbon monoxide gas intermediate **I** is converted into acylpalladium species (**II**). Further, nucleophilic attack of anthranilic acid on acylpalladium species (**II**) generates intermediate **III**, which on reductive elimination gives **IV**. Finally, intermediate **IV** undergoes intramolecular cyclization to provide the desire product **3a** via elimination of water molecule.

In conclusion, a simple and efficient $PdCl_2(PhCN)_2$/$P(tBu)_3{\cdot}HBF_4$-catalyzed carbonylative synthesis of the benzoxazinone derivatives via the aminocarbonylation of anthranilic acid with aryl bromide has been documented. This method serves as an efficient alternative to the classical approaches for the synthesis of benzoxazinone. The simple starting materials and tolerance of wide range of functional groups demonstrated the practical utility of this protocol. Further, the developed method could also be extended successfully for the synthesis of quinazolinone derivatives.

## Experimental Section

### General procedure for the synthesis of benzoxazinones (3a–3t) from anthranilic acid:

To a 100 mL stainless steel high pressure reactor, anthranilic acid (1 mmol), aryl bromide (1.15 mmol), DABCO (2 mmol), $PdCl_2(PhCN)_2$ (3 mol%), and $P(tBu)_3{\cdot}HBF_4$ (12 mol%) were added in anhydrous toluene (10 mL). The 400 mg activated 3 Å MS were added to the reaction mixture and the autoclave was closed. The autoclave was purged three times with carbon monoxide, pressurized with CO 200 psi at ambient temperature. The reaction mixture was stirred with a mechanical stirrer (500 rpm) at 100 °C for 24 h. After completion of reaction, the reactor was cooled to room temperature and the remaining CO was carefully vented. The reactor vessel was




**Scheme 4.** Direct synthesis of quinazolinones from anthranilic acid.

washed with ethyl acetate (3×10 mL) to remove traces of product and catalyst, if present. The ethyl acetate layer was washed with water (2×10 mL), dried over $Na_2SO_4$, and the solvent was evaporated under vacuum. The crude residue was purified by column chromatography on silica gel using ethyl acetate/petroleum ether as an eluent to give corresponding the benzoxazinones.

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**Keywords:** anthranilic acid · aryl bromides · benzoxazinones · carbonylation · quinazolinones

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