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Carbonylation of anthranilic acid with aryl and hetero aryl bromides as a concise way towards benzoxazinone derivatives

Sujit P. Chavan[a] and Bhalchandra M. Bhanage*[a]

Abstract: A simple and efficient, $PdCl_2(PhCN)_2/P(t\text{-Bu})_3 \cdot HBF_4$ catalyzed carbonylative cyclization of anthranilic acid with aryl bromide was investigated for the synthesis of benzoxazinones under mild reaction condition. The developed protocol has been extended for the synthesis of quinazolin-4(3H)-ones. Furthermore, the tolerance of wide range of functional group on anthranilic acid as well as on aryl bromide demonstrates the practical utility of the protocol.

Benzoxazinones 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 benzoxazinones involves the condensation of anthranilic acid with acid chlorides or acid anhydrides. However, the use of hazardous chemicals, harsh reaction condition 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 process for the synthesis of carbonyl compounds. Hence, several facial approaches has been well documented in literature using palladium catalyzed carbonylation reaction for synthesis of 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-worker for the synthesis of benzoxazinones.[7] Beller and co-workers has reported similar approach for the synthesis of benzoxazinones using 2-bromoanilines with aryl bromides.[8] Furthermore, Alper and co-workers reported palladium catalyzed carbonylation of 2-iodoanilines with acid chlorides for the synthesis of benzoxazinones. The analogous phosphine ligand free reaction was developed by Li and co-worker using Pd-NHC catalytic system.[9] In addition, Beller group developed K_2PdCl_4/n-butyldiadamantylphosphine catalyzed protocol for the synthesis of 2-alkylbenzoxazinones *via* carbonylative coupling of 2-bromoanilines with symmetrical acid anhydrides.[10] In recent year, several transition metal catalyzed carbonylative C-H activation approaches has 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 inexpensive and easily available feedstocks.
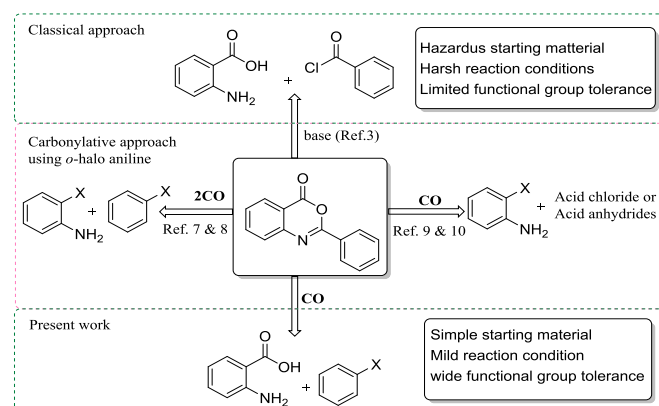
Scheme 1. Classical and carbonylative approach for the synthesis benzoxazinones.

In continuation with our current research interest on the development of palladium catalyzed carbonylation reaction for the synthesis of 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 $PdCl_2(PhCN)_2/P(t\text{-Bu})_3 \cdot HBF_4$ catalyzed carbonylation of anthranilic acid with aryl halides (Fig. 1). The scope of this methodology was further extended for the cascade synthesis of 2-arylquinazolinones and amino acid derived quinazolin-4(3H)-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 DABCO as a base in anhydrous toluene and it was observed that the desire product was formed in very poor yield (Table 1, entry 1). The properties of ligand like cone angle, bite angle and basicity has major contribution for 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 significant role in the palladium-catalyzed cross-coupling reactions. Hence, we have screened wide range of phosphine ligands. At the beginning, addition of dppf led to increase in the yield of **3a** along with the formation of 4-methoxybenzoic acid in significant amount *via* the hydroxy carbonylation of 2**a** (Table 1, entry 2). The water required for the hydroxy carbonylation may come from the condensation of IV (Scheme 3), 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

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desire product in some extent (Table 1, entry 3). Subsequently, other phosphine ligands such as Xantphos, P(t-Bu)$_3$·HBF$_4$, DevPhos and SPhos were also screened for this reaction (Table 1, entries 4–7). Among all, P(t-Bu)$_3$·HBF$_4$ performed as a best ligand providing 78% yield of the desired product (Table 1, entry 5).

evaluated. A variety of aryl bromides reacts with range of anthranilic acid to produce corresponding benzoxazinones in a good to excellent yield (Table 2). The model reaction gave 92% as isolated yield of the **3a**. 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

Table 1. Screening of Reaction Parameter^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(t-Bu)$_3$·HBF$_4$	DABCO	78
6	Pd(OAc)$_2$	DevPhos	DABCO	48
7	Pd(OAc)$_2$	SPhos	DABCO	54
8	Pd(dba)$_2$	P(t-Bu)$_3$·HBF$_4$	DABCO	73
9	**PdCl$_2$(PhCN)$_2$**	**P(t-Bu)$_3$·HBF$_4$**	**DABCO**	**94**
10	PdCl$_2$(PPh$_3$)$_2$	P(t-Bu)$_3$·HBF$_4$	DABCO	64
11	Pd(PPh$_3$)$_4$	P(t-Bu)$_3$·HBF$_4$	DABCO	55
12	PdCl$_2$(PhCN)$_2$	P(t-Bu)$_3$·HBF$_4$	NEt$_3$	45
13	PdCl$_2$(PhCN)$_2$	P(t-Bu)$_3$·HBF$_4$	DBU	81
14	PdCl$_2$(PhCN)$_2$	P(t-Bu)$_3$·HBF$_4$	NaOAc	10
15	PdCl$_2$(PhCN)$_2$	P(t-Bu)$_3$·HBF$_4$	K$_2$CO$_3$	30
16	PdCl$_2$(PhCN)$_2$	P(t-Bu)$_3$·HBF$_4$	Na$_2$HPO$_4$	18

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

Table 2. Table Substrate scope for the synthesis of benzoxazinones^a.

[a] Reaction conditions: **1a-1d** (1 mmol), **2a-2p** (1.15 mmol), PdCl$_2$(PhCN)$_2$ (3 mol%), P(t-Bu)$_3$·BF$_4$(12 mol%), DABCO (2 mmol) and molecular sieves (3Å) were added in toluene (10 mL) then the reaction mixture was stirred for 24 h at 100 °C. [b] Isolated yields.

Next, we screened a range of palladium precursors with P(t-Bu)$_3$·HBF$_4$ as ligand (Table 1, entries 8–11), among them PdCl$_2$(PhCN)$_2$ gave **3a** in 94% yield (Table 1, entry 9). Our previous findings reveals 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 like NEt$_3$ and DBU and inorganic bases such as NaOAc, K$_2$CO$_3$ and Na$_2$HPO$_4$ were found to be less effective (Table 1, entries 12–16). Using these optimized reaction parameters, the scope and limitations of developed protocol was

respective products (Table 2, **3a–3d**). Furthermore, the aryl bromide bearing electron-withdrawing groups such as –NO$_2$, –F, –CN and –COCF$_3$ were tested under optimized reaction condition. It was noted that the –NO$_2$ group provided less yields of the corresponding products (Table 2, **3e** and **3f**), while other electron-withdrawing substituents such as –F, –CN and –COCF$_3$ offered desired products in good yields (Table 2, **3g–3k**). The carbonylative cyclization of anthranilic acid with bromobenzene produces the 96% yield of 2-phenyl-4H-benzo[d][1,3]oxazin-4-one (**3l**). Moreover, heterocyclic aryl bromides such as 4-bromopyridine and 3-bromoisoquinoline were also found to be

compatible under the present catalytic system (Table 2, **3m** and **3n**). In addition to this, 3-bromostyrene and 4-bromostyrene could also be converted into respective products **3o** (Figure 1, CCDC 1478766) and **3p**. 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 a good to excellent yields.
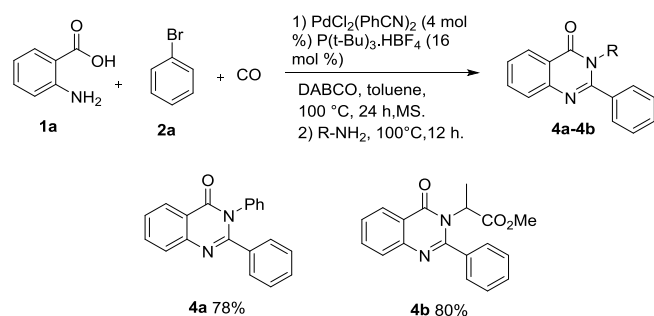

Scheme 2. Direct synthesis of quinazolinones from anthranilic acid.

The present methodology was further extended for the synthesis of 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 in reaction mixture and heated at 100 °C for 12 h to furnish the quinazolinones **4a** and **4b** (Scheme 2).
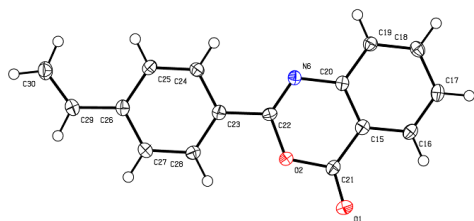
Figure 1. X-ray structure of compound **3o**.

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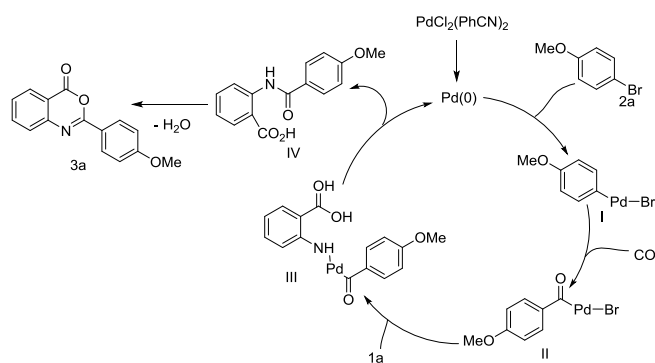
Scheme 3. Plausible reaction mechanism for the synthesis of benzoxazinones.

In conclusions, a simple and efficient PdCl$_2$(PhCN)$_2$/P(*t*-Bu)$_3$·HBF$_4$ catalyzed carbonylative synthesis of the benzoxazinone derivatives *via* the aminocarbonylation of anthranilic acid with aryl bromide has been documented. Present methodology serves as an efficient alternative to the classical approaches for 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 methodology could also be extended successfully for the synthesis of quinazolinone derivatives.

Experimental Section

General procedure for the synthesis 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(*t*-Bu)$_3$·HBF$_4$ (12 mol%) were added in 10 mL anhydrous toluene. The 400 mg activated 3Å MS were added in 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 temperature 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 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$_2$SO$_4$ and the solvent was evaporated under vacuum. The crude residue was purified by column chromatography on silica gel using ethyl acetate/petroleum ether as eluents to give corresponding benzoxazinones.

Acknowledgements

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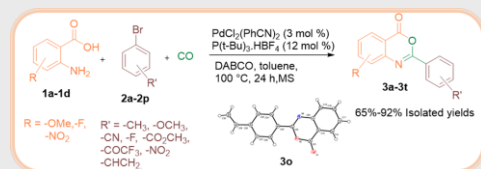
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A simple and efficient $PdCl_2(PhCN)_2/P(t\text{-Bu})_3 \cdot HBF_4$ catalyzed carbonylative cyclization of anthranilic acid with aryl bromide was investigated for the synthesis of benzoxazinones under mild reaction condition.