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ARTICLE TYPE

Highly-Efficient Palladium-Catalyzed Aminocarbonylation/S_NAr Approach to Dibenzoxazepinones

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A convenient procedure for the synthesis of dibenzoxazepinones has been developed. Utilizing the protocol of one-pot palladium-catalyzed aminocarbonylation/aromatic nucleophilic substitution (S_NAr) sequence, with 2-aminophenols and 2-bromofluorobenzenes as the substrates, the desired dibenzo[*b*,*e*][1,4]oxazepin-11(5*H*)-ones were prepared in moderate to excellent yields. The broad substrate scope and functional group tolerance of the reaction makes this approach a practical method for the synthesis of valuable dibenzoxazepinone and its derivatives. Mechanistic studies suggest that aminocarbonylation proceeds prior to S_NAr.

Introduction

Seven-membered heterocycles are receiving continuing attention as their skeletons are widely present in numerous pharmaceuticals and natural products.[1] Among these seven-membered heterocycles, dibenzo[*b*,*e*][1,4]oxazepin-11(5*H*)-one derivatives represents a class of versatile compounds owing to their promising pharmaceutical and biological activities, including HIV-1 RT inhibition,[2] H_4R agonist,[3] antidepressant (Figure 1), anti-psychotic,[4] anti-tumor,[5] antioxidant[6] and anti-inflammatory[7] activities. Motivated by the importance of these compounds, many procedures have been developed for their preparation. Since the first report on the synthesis of dibenzoxazepinone derivatives in 1964,[8] conventional routes to dibenzoxazepinones and their derivatives usually involve classical, several steps procedure through the intermolecular cyclization of *ortho*-aminophenols with *ortho*-halogen benzonic acids[3,9] or *ortho*-nitro benzonic acids[10], or through reduction-lactamization sequence,[11] Among these routes, the isolation of intermediates and severe conditions (usually involving strong inorganic bases and harsh reaction conditons) are two obstacles to high efficiency and wide functionality tolerance. Although a series of alternative protocols such as intramolecular Friedel–Crafts acylation,[12] oxidation of dibenzo(*b*,*f*)(1,4)-oxazepines,[13] Beckmann rearrangement,[14] Ugi four-component reaction,[15] Smiles rearrangement,[16] Ru-catalyzed C-H hydroxylation,[17] palladium-catalyzed C-N cross coupling[18] and palladium-catalyzed intramolecular carbonylation[19] have been described to prepare dibenzoxazepinones, their substrates need to be prepared beforehand. Thus it can be seen that developing general and highly-efficient access to dibenzoxazepinones from commercially available reagents still remains a challenge and interesting topic for organic synthesis.

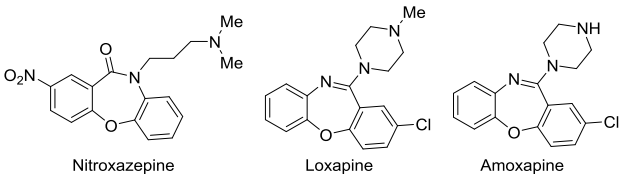

Figure 1. Selected antidepressant drugs with dibenzoxazepinone skeleton.

In transition metal-catalyzed transformations, palladium-catalyzed carbonylations have already become a true toolbox in modern organic synthesis. Since the seminal work of Heck and co-workers in 1974,[20] impressive progress has been achieved in palladium-catalyzed carbonylation reactions after 40 years' development.[21] Through palladium-catalyzed carbonylations, carbon monoxide (CO), one of the cheapest C*1* sources, can be installed into the parent molecules. In this way, synthetically important and valuable carbonyl-containing compounds are readily accessible, which can be submitted for further modifications. Based on our continual interest concerning palladium-catalyzed carbonylative synthesis of heterocycles[22] and the fusion of carbonylation and nucleophilic substitution reactions,[23] we intended to develop a facile one-pot protocol with mild conditions for the preparation of dibenzoxazepinones from readily available reagents in virtue of palladium-catalyzed aminocarbonylation and aromatic nucleophilic substitution (S_NAr).

Results and Discussion

Initially, 2-bromofluorobenzene (**1a**) and 2-aminophenol (**2a**) were selected as the model substrates to optimize the reaction conditions (Table 1). A preliminary study was carried out on a 0.5 mmol scale at 120 ^{0}C in DMAc, using $BuPAd_2$ as the ligand and DBU as the base, affording **3a** in 75% isolated yield (Table 1, entry 1). Based on this preliminary result, further investigation on solvents, bases, temperatures, reaction time, catalyst loading and

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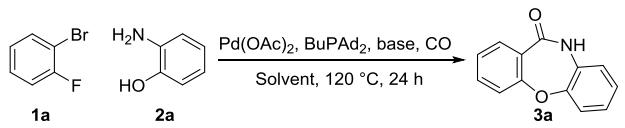
CO pressure were conducted. Among the tested common polar aprotic solvent (Table 1, entries 2, 3, 4, and 5), we found the best yield was achieved in DMSO and the reaction time can be shortened to 24 hours. Non-polar aprotic solvents such as 1,4-dioxane and toluene are not suitable for this reaction (Table 1, entries 6 and 7). This can be rationalized by the fact that intramolecular or intermolecular S_N2 substitution is more favoured in the polar aprotic solvent.[23] Then two other kinds of organic tertiary amines were applied as bases (Table 1, entries 8 and 9), and no better performance was found than DBU. The similar effect was observed when inorganic base K_2CO_3 was used (Table 1, entry 10), which was probably due to the poor solubility of K_2CO_3 in DMSO. No dibenzo[*b*,*e*][1,4]oxazepin-11(5*H*)-one was observed when $BuPAd_2$ was replaced with DPPP in MeCN solution (detailed results in Table S1 of Supporting Information). This phenomena resembles a recent report.[25] Reducing palladium catalyst loading or lowering CO pressure result in a drop in yield; decreasing the reaction temperature also resulted in the yield decline (detailed results in Table S1 of Supporting Information).

Table 1. Optimization of reaction conditions.[a]



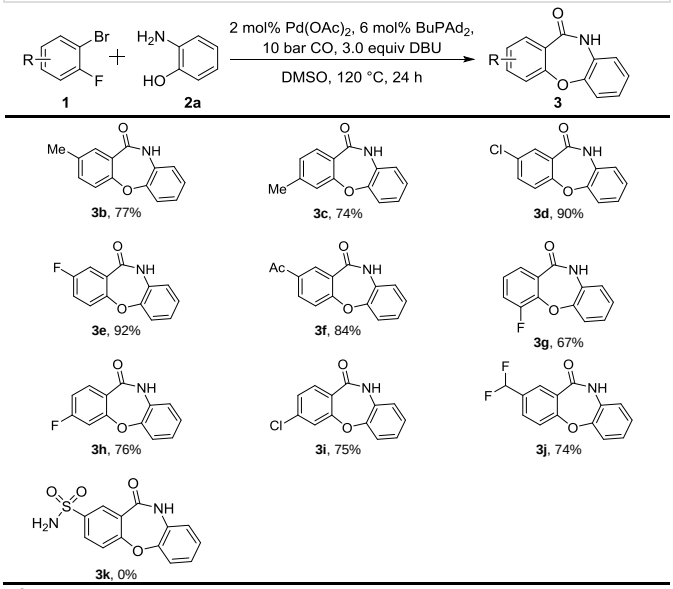
1a 2a 3a

Entry	CO (bar)	Base	Solvent	Yield[b]
1	10	DBU	DMAc	78 (75)[c]
2	10	DBU	DMF	34
3	10	DBU	NMP	58
4	10	DBU	DMSO	86 (82)
5	10	DBU	MeCN	25
6	10	DBU	1,4-dioxane	19
7	10	DBU	toluene	0
8	10	DABCO	DMSO	51
9	10	DIPEA	DMSO	70
10	10	K_2CO_3	DMSO	43

[a] Unless otherwise stated, the reaction was conducted on 0.50 mmol scale (2mol% $Pd(OAc)_2$, 6 mol% $BuPAd_2$, 0.50 mmol of **1a**, 0.50 mmol of **2a**, 1.5 mmol base) with 2.0 mL solvent. Reaction temperature was 120 ^{0}C. Reaction time was 24 h. [b] Yields were determined by GC with hexadecane as an internal standard; yields in parentheses are for the isolated product. [c] Reaction time was 32 h. Ad = adamantyl, Bu = *n*-butyl, DABCO =1,4-diazabicyclo[2.2.2]octane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIPEA = *N*,*N*'-diisopropylethylamine, DMAc = *N*,*N*-dimethylacetamide, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, NMP = *N*-methyl-2-pyrrolidone.

With the optimized reaction conditions in hand, we further investigated the substrates scope of this procedure. Several substituted 2-bromofluorobenzenes were subjected to the optimized conditions described above. As shown in Table 2, a range of 2-bromofluorobenzene possessing methyl, halogen, difluoromethyl or acetyl (all commercially available), which is incompatible with strong basic conditions, at various positions were tolerated and the desired dibenzoxazepinones were obtained in moderate to good yields (**3b**-**3j**). It is noted that the electron-withdrawing carbonyl group in the product **3h** and **3i** has no activating effect to the fluorine and chlorine at *para*-position.[23] The reaction product **3d** is the precursor of antidepressant drug Loxapine and Amoxapine.[3,8c] However when this protocol was applied to 3-bromo-4-fluorobenzenesulfonamide, no corresponding product (**3k**) was observed, although the substrate was consumed.

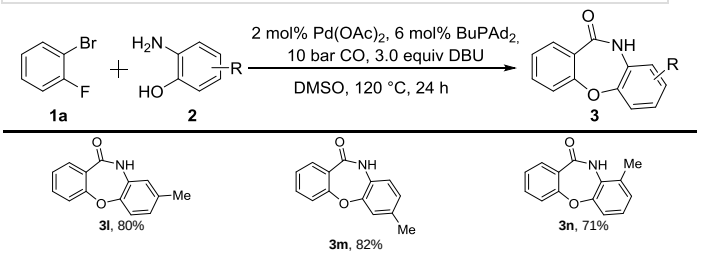
Table 2. Substrate scope of 2-bromofluorobenzenes.[a]



[a]All reactions were conducted under conditions: **1** (0.5 mmol), **2a** (0.5 mmol), DBU (1.5 mmol), 2 mol% $Pd(OAc)_2$, 6 mol% $BuPAd_2$, DMSO (2.0 mL), 10 bar CO, 120 ^{0}C and 24 h. Yield of the isolated product.

Then the scope of substituted 2-aminophenols were investigated (Table 3). Compared with the results of 4 or 5-methyl substituted 2-aminophenol (**3l**, **3m**), the yield of reaction with 3-methyl substituted 2-aminophenol (**3n**) was lower, which can be attributed to the steric hindrance that has been previously reported.[27] The 2-aminophenols bearing electron-withdrawing groups are tolerated (**3o**, **3p**). However when the secondary aniline 2-(phenylamino)phenol was employed, no desired product **3q** was formed. This also can be explained by crowed environment on the nitrogen atom and also the stability and therefore lack of reactivity of the in situ formed N-Ph anion.

Table 3. Substrate scope of 2-aminophenols.[a]



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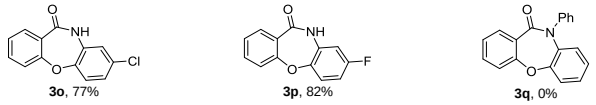
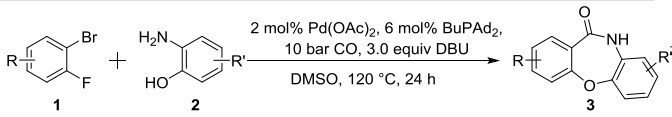
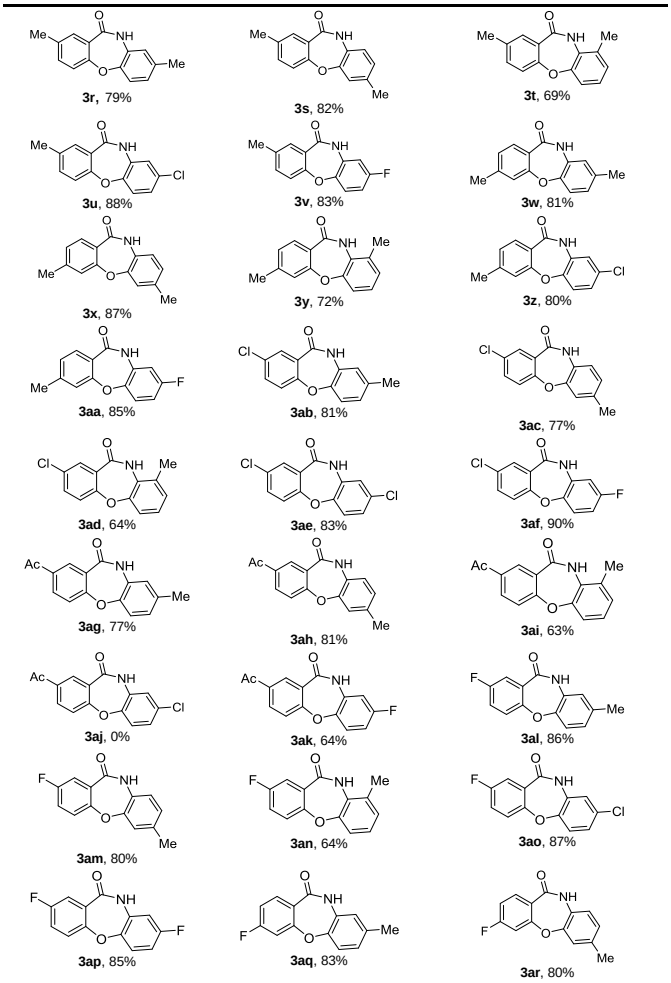


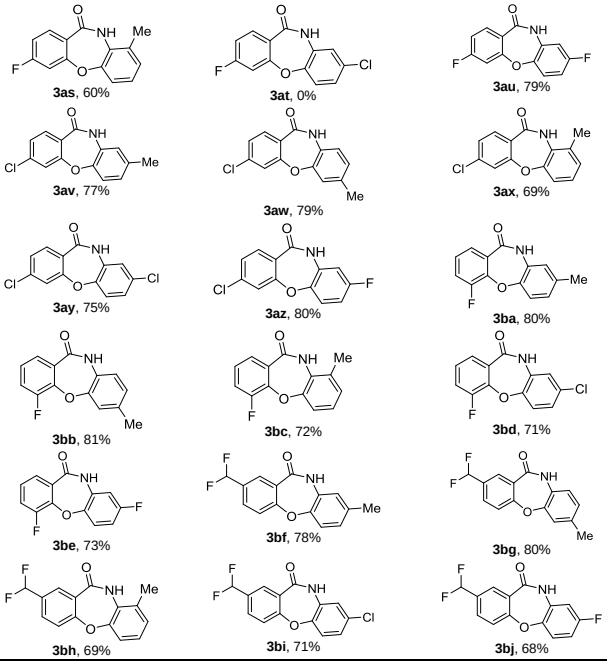
[a] All reactions were conducted under conditions: **1** (0.5 mmol), **2** (0.5 mmol), DBU (1.5 mmol), 2 mol% $Pd(OAc)_2$, 6 mol% $BuPAd_2$, DMSO (2.0 mL), 10 bar CO, 120 ^{0}C and 24 h. Yield of the isolated product.

To prove the broad-spectrum on substrates of this protocol, combinatorial reactions of various substituted 2-aminophenols with various substituted 2-bromofluorobenzenes were conducted (Table 4). As shown in Table 4, except two examples **3aj** and **3at**, moderate to good yields were achieved for the other substituted 2-aminophenols and substituted 2-bromofluorobenzenes. It shows that the protocol has good tolerance to diverse functional groups at different position of the dibenzoxazepinone motif. Among these products, some of them such as **3u**, **3z**, **3ao** and **3at** may potentially be applied as intermediates to prepare some analogues of Clozapine.[3]

Table 4. Reaction of substituted 2-aminophenols with substituted 2-bromofluorobenzenes.[a]



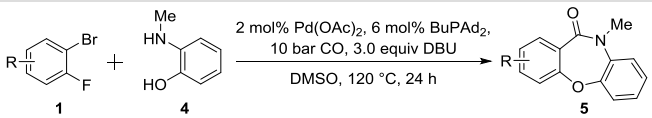


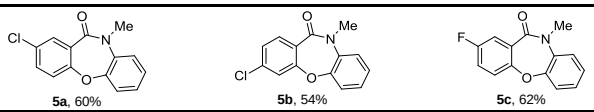


[a] All reactions were conducted under conditions: **1** (0.5 mmol), **2** (0.5 mmol), DBU (1.5 mmol), 2 mol% $Pd(OAc)_2$, 6 mol% $BuPAd_2$, DMSO (2.0 mL), 10 bar CO, 120 ^{0}C and 24 h. Yield of the isolated product.

Considering that to date, to the best of our knowledge, there are only several reported examples involving Pd-catalyzed aminocarbonylation of aryl halides with secondary amine for the preparation of tertiary amides[27,28] and only two examples for aminocarbonylation of aryl bromide with *N*-methyl aniline,[28a] aminocarbonylation of aryl bromide with *N*-alkyl aniline is still a challenging issue. So we selected 2-(methylamino)phenol as nucleophilic reagent to further extend the scope of reaction substrates (Table 5). To our delight, the reactions between 2-(methylamino)phenol **4** and some electron-withdrawing group substituted 2-bromofluorobenzenes **1** proceeded smoothly to give the desired products in moderate yields (**5a**, **5b**, **5c**).

Table 5. Reaction of substituted 2-aminophenols with 2-(methylamino)phenol.[a]





[a] All reactions were conducted under conditions: **1** (0.5 mmol), **4** (0.5 mmol), DBU (1.5 mmol), 2 mol% $Pd(OAc)_2$, 6 mol% $BuPAd_2$, DMSO (2.0 mL), 10 bar CO, 120 ^{0}C and 24 h. Yield of the isolated product.

Finally, in order to clarify the sequence of this palladium-catalyzed aminocarbonylation and aromatic nucleophilic substitution reactions and propose a plausible mechanism, some control experiments based on the model reaction were conducted (Scheme 1). Under the optimized conditions without Pd-catalyst, no reaction product **7** or **8** was detected and no conversion of both substrates was observed (Scheme 1a). It indicates that Pd-

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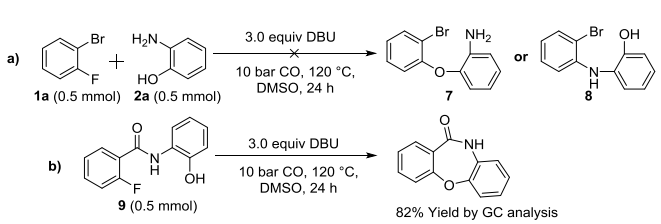
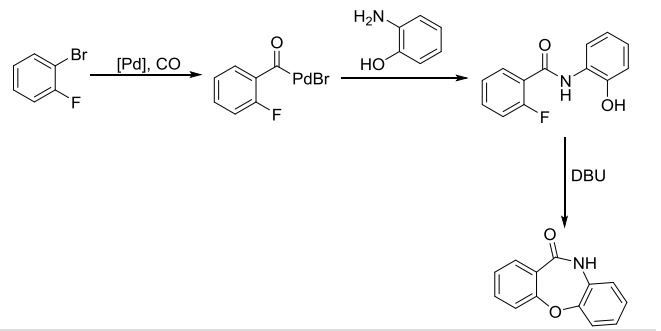
catalyzed aminocarbonylation occurs prior to the aromatic nucleophilic substitution. Therefore we inferred that 2-fluoro-*N*-(2-hydroxyphenyl)benzamide should be the plausible intermediate of reaction. Although some measures to obtain the intermediate including reducing the catalyst loading, lowering temperature, changing base and shortening reaction time were taken for detecting the *in-situ* generated amide intermediate, the amide intermediate was not observed by GC and GC-MS analysis. Then the plausible amide **9** intermediate was prepared according to the literature method.[3] As expected, the amide **9** was converted to the product under the conditions without the Pd-catalyst (Scheme 1b), which not only indirectly confirms that the amide **9** is the reaction intermediate, but also proves that DBU plays as base both in the aminocarbonylation and in the S_NAr.



Scheme 1. Control experiments.

Based on the results of control experiments, a plausible mechanism is given in Scheme 2. Firstly, acylpalladium species is formed from 2-bromofluorobenzene through oxidative addition with Pd(0). Subsequently, the amide intermediate is generated from the reaction between 2-aminophenol and acylpalladium complex. Finally, under the basic conditions, the fluorine atom acts as a leaving group with the help of the carbonyl group at *ortho*-position and the S_N2 type aromatic nucleophilic substitution occurs and the product is formed.



Scheme 2. Proposed Reaction Mechanism.

Conclusions

In conclusion, a mild one-pot protocol for the synthesis of dibenzo[*b*,*e*][1,4]oxazepin-11(5*H*)-ones from commercially-available starting materials has been developed. In the presence of palladium catalyst and base, with 2-fluorobromobenzenes and 2-aminophenols as substrates, the desired dibenzoxazepinones were obtained in moderate to excellent yields *via* tandem aminocarbonylation/S_NAr approach. Several control experiments were performed and a possible reaction mechanism is proposed.

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General Considerations

NMR spectra were recorded on a 300 MHz spectrometer at 295 K in $CDCl_3$ or DMSO. Chemical shifts (parts per million) are given relative to solvent. References for $CDCl_3$ were 7.26 ppm (^{1}H NMR) and 77.00 ppm (^{13}C NMR); references for [D_6]DMSO were 2.50 ppm (^{1}H NMR) and 40.00 ppm (^{13}C NMR). High-resolution mass spectrometry (HRMS) was performed using an ESI-TOF/MS instrument. The products were isolated from the reaction mixture by column chromatography on silica gel 60 (0.063−0.2 mm, 70−230 mesh).

Representative procedure for the synthesis of dibenzoxazepinones

A vial (6 mL) was charged with $Pd(OAc)_2$ (2 mol%), $BuPAd_2$ (6 mol%), 2-aminophenol (0.5 mmol) and a magnetic stirring bar. Then, 1-bromo-2-fluorobenzene (0.5 mmol), DBU (3.0 equiv), and DMSO (2.0 mL) were injected under argon by syringe. 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 argon atmosphere. After flushing the autoclave three times with CO, a pressure of 10 bar of CO was adjusted at ambient temperature. Then, the reaction was performed for 24 h at 120^{0}C. After the reaction was complete, the autoclave was cooled down with ice-water mixture to room temperature and the pressure was released carefully. The solution was diluted with ethyl acetate and then silica gel was added into the solution. After evaporation of the organic solvent, the crude product was purified by column chromatography using ethyl acetate/n-pentane.

Notes and references

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† Electronic Supplementary Information (ESI) available: [reaction procedure and analytic data]. See DOI: 10.1039/b000000x/

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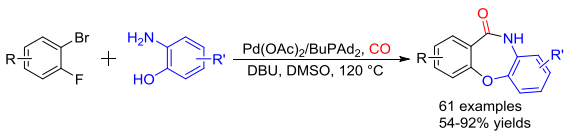

A practical protocol for the synthesis of dibenzo[*b*,*e*][1,4]oxazepin-11(5*H*)-ones has been developed. In virtue of Pd-catalyzed aminocarbonylation and aromatic nucleophilic substitution, 61 examples of the desired dibenzoxazepinones were obtained in moderate to excellent isolated yields (54-92%).