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Palladium-catalysed regioselective *N*-arylation of anthranilamides: A tandem route for dibenzodiazepinone synthesis

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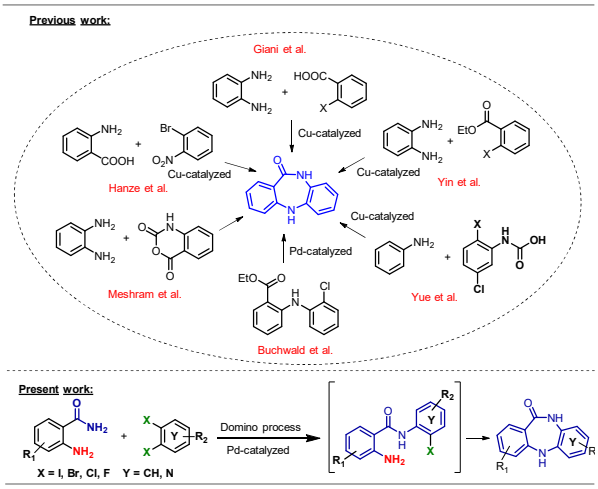
A palladium-catalyzed domino approach to the synthesis of 10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepinones from 2-aminobenzamides and 1,2-dihaloarenes has been developed. Our strategy integrating double *N*-arylations (inter- and intra-molecular) of 2-aminobenzamides with 1,2-dihaloarenes under palladium-catalyzed condition is clearly distinct from the current literature available for the synthesis of dibenzodiazepinones. Unlike a previous report described for regioselective *N*-arylation of 2-aminobenzamide at amine group, our mechanistic studies support regioselective *N*-arylation of 2-aminobenzamide occurs first primarily at the amide group. The translational application of our protocol may be demonstrated to the synthesis of a marketed drug, clozapine.

Introduction

10,11-Dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepinones are particularly an important class of nitrogen heterocycles exhibiting considerable pharmaceutical applications as antipsychotic, anti-anaphylatic, and anxiolytic agents.[1] Dibenzodiazepinones have been known to act as histone deacetylase inhibitor,[2] and Chk1kinase inhibitor.[3] The scaffold has emerged as a key component of various antipsychotic drugs, e.g.; clozapine, dibenzepin, pirenzepine, etc.[4] In particular, clozapine has gained attention over the years due to lack of its extrapyramidal side effects, and for treating the patients with drug resistant schizophrenia.[5]

Reported routes for dibenzodiazepinones largely rely on the formation of a key lactam intermediate (Scheme 1).[6,7] In 1963, Hanze et al. reported a multi-step synthesis of dibenzodiazepinone from anthranilic acid and 2-bromonitrobenzene in the presence of a copper-catalyst leading to overall poor yield of dibenzodiazepinone.[8] Giani et al.[9] and Yin et al.[10] independently reported the synthesis of dibenzodiazepinone from *o*-phenylenediamine and 2-halobenzoates or o-halobenzoic acid in the presence of a copper-catalyst. Yue et al. disclosed the synthesis of diabenzodiazepinone from aniline and (2-halo-5-chlorophenyl) amino acid using a copper-catalyst.[11] Meshram et al. reported the condensation and in situ cyclization of the reaction of *o*-phenylenediamine and substituted isatoic anhydrides to give diabenzodiazepinone.[12] Remarkably, palladium catalyzed reactions for the synthesis of diabenzodiazepinone remains under developed.

In 2011, Buchwald et al. reported the reaction of 2-aminobenzophenone and 2-bromochlorobenzene in the



Scheme 1:- Approaches for the synthesis of dibenzodiazepinones

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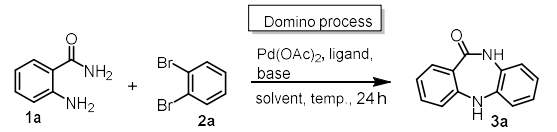
presence of a palladium-catalyst to form diarylamine, which upon further reaction gave dibenzodiazepinone.[13] While some copper-catalyzed, especially tandem reactions have certain advantages, a palladium-catalyzed domino reaction to the synthesis of dibenzodiazepinones from readily available starting material is yet to be realized. While *N*-arylation of anilines[14] and benzamides[15] using aryl halides have been studied well both under palladium-[16] or copper-catalysis,[17] regioselective *N*-arylation of 2-aminobenzamides that contain both the functional groups has been the subject of least investigation. Buchwald et al. has shown that regioselective *N*-arylation of 2-aminobenzamides with bromobenzene could occur at amine group under palladium catalysis and at amide group under copper-catalysis.[18] Subsequently, Lui et al. reported *N*-arylation at amine group (a reverse regioselectivityto that observed in Buchwald's reaction under copper-catalysis) in the reaction of 2-aminobenzamide and arylboronic acid under copper-catalysis.[19] Inspired by these two reports and our own interest in the domino reactions to the synthesis of nitrogen heterocycles,[20] we envisaged that regioselective sequential double *N*-arylations of 2-aminobenzamide with 1,2-dibromobenzene could give dibenzodiazpinone.

Our continued interest prompted us to develop a domino approach to the synthesis of 10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepinones by using 2-aminobenzamide and 1,2-dibromobenzene under palladium-catalysis. The reverse regioselectivity of *N*-arylation at amide group observed in our study made this work distinct from the Buchwald's reaction under palladium-catalysis.

Results and discussion

Initially, a one-pot domino approach was explored that involved 2-aminobenzamide and 1,2-dibromobenzene as the two coupling partners to prepare dibenzodiazepinone.

Table 1. Optimization study for the synthesis of dibenzodiazepinone.



Entry	Pd-catalyst	Ligand	Base	Solvent	Temp.	%Yield
1	$Pd(OAc)_2$	rac-BINAP	K_2CO_3	Toluene	110° C	0
2	$Pd(OAc)_2$	PPh_3	NaOBu-t	Toluene	110° C	0
3	$Pd(OAc)_2$	PPh_3	K_2CO_3	Toluene	110° C	0
4	$Pd(OAc)_2$	PCy_3	K_2CO_3	Toluene	110° C	30
5	$Pd(OAc)_2$	rac-BINAP	K_2CO_3	DMF	110° C	20
6	$Pd(OAc)_2$	S-Phos	K_2CO_3	Toluene	110° C	65
7	$Pd(OAc)_2$	Xant-Phos	K_2CO_3	Toluene	110° C	55
8	$Pd(OAc)_2$	S-Phos	Cs_2CO_3	Toluene	110° C	60
9	$Pd(OAc)_2$	S-Phos	K_2CO_3	*o*-xylene	140° C	35
10	$PdCl_2$	S-Phos	K_2CO_3	Toluene	110° C	20
11	$Pd(TFA)_2$	S-Phos	K_2CO_3	Toluene	110° C	0
12	$Pd(acac)_2$	S-Phos	K_2CO_3	Toluene	110° C	0

Reaction conditions: 2-aminobenzamide **1a** (0.5 mmol), 1,2-dibromobenzene **2a** (0.5 mmol), $Pd(OAc)_2$ (10 mol%), ligand (20 mol%), base (3 equiv.), solvent (1 mL), 110 °C, 24 h

Heating 2-aminobenzamide and 1,2-dibromobenzene in the presence of $Pd(OAc)_2$, rac-BINAP, and K_2CO_3 in toluene at 110 °C for 24 h did not result in the formation of any cyclized product (Table 1, Entry 1). Likewise, a different ligand PPh_3 and base NaOBu-t also proved to be ineffective (Entry 2). Changing the base from NaOBu-t to K_2CO_3 also did not result in the formation of the cyclized product (Entry 3). However, another ligand PCy_3

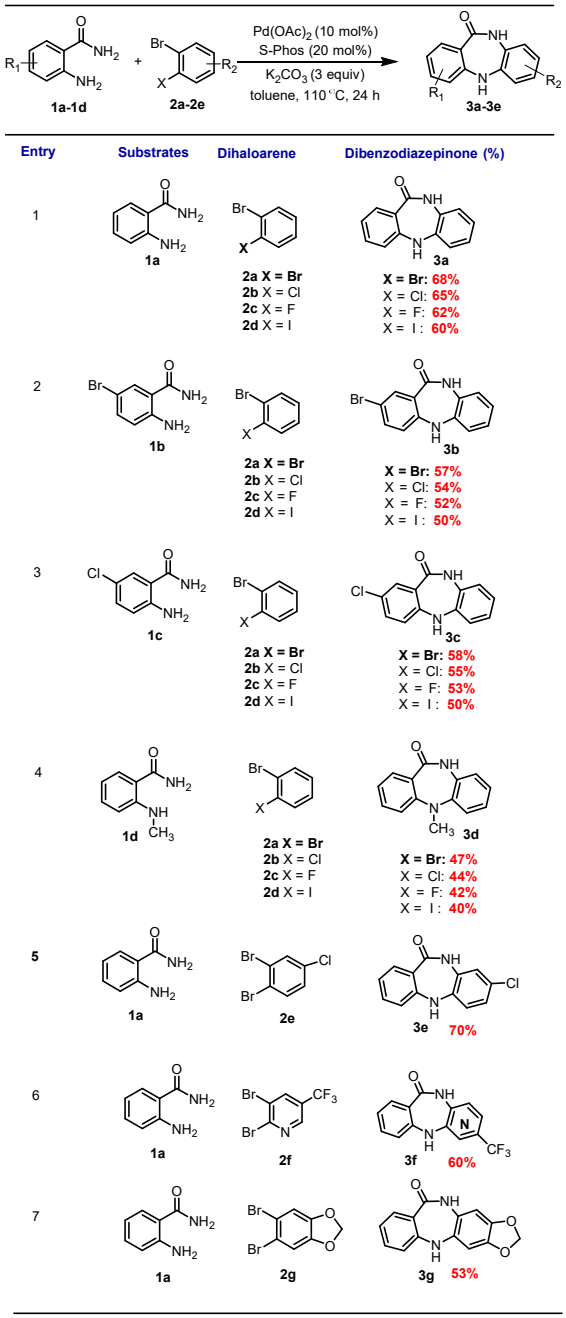


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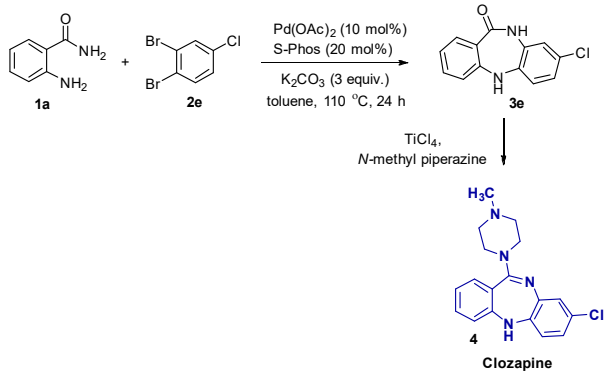
Table 2. Synthesis of various substituted dibenzodiazepinones.

produced dibenzodiazpinone in 30% yield (Entry 4). Reaction of **1a** and **2a** in presence of $Pd(OAc)_2$, rac-BINAP, and K_2CO_3 in DMF at 110 °C for 24 h also produced the cyclized product only in 20% yield (Entry 5). Further change of ligand from rac-BINAP to S-Phos resulted in an efficient conversion of the reaction yielding 65% yield of the product (Entry 6). The ligand Xant-Phos exhibits nearly a comparable effect delivering the product **3a** in 55% yield (Entry 7). Retaining the S-Phos as ligand produced similar result in the presence of Cs_2CO_3 as a base (Entry 8). Finally, raising the temperature to 140 °C did not improve the yield (Entry 9). Changing the catalyst from $Pd(OAc)_2$ to $PdCl_2$, significantly decreases the formation of cyclized product (Entry 10). Catalysts like $Pd(TFA)_2$ and $Pd(acac)_2$ did not give the desired product (Entry 11-12). Remarkably, the formation of *N*-monoarylated product in some of these reactions proposes that the reaction follows a domino reaction pathway.

Next, the scope of substituted 2-aminobenzamides (**1a-d**) and various 1,2-dihaloarenes (**2a-e**) was investigated (Table 2). Similar to 1,2-dibromobenzene, 1-bromo-2-chlorobenzene, 1-bromo-2-iodobenzene and 1-bromo-2-fluorobenzene all reacted with 2-aminobenzamide (**1a**) eventfully yielding **3a** in 60-68% yield (Entry 1).

It is likely that N-arylation of amine could occur with 1-bromo-2-fluorobenzene via a nucleophilic substitution. However, reaction of 2-amino-5-bromobenzamide (**1b**) and 1,2-dihaloarenes (**2a-2d**) under the optimized condition gave the cyclized product (**3b**) in relatively reduced (50-57%) yield (Entry 2). Notably, no debromination was observed under the optimized condition demonstrating further synthetic utility of the protocol. Similarly, 2-amino-5-chlorobenzamide (**1c**) reacted with different 1,2-dihaloarenes (**2a-2d**) under the optimized condition delivering the cyclized product (**3c**) in 50-58% yield (Entry 3). To further extend the substrate scope, the reaction of *N*-methylbenzamide (**1d**) and 1,2-dihalobenzene (**2a-2d**) was investigated, which upon isolation gave the cyclized product (**3d**) in 40-47% yield (Entry 4). 2-aminobenzamide (**1a**) and 1,2-dibromo-4-chlorobenzene (**2e**) were reacted successfully under the standard condition to obtain the cyclized product (**3e**) in 70% yield (Entry 5).

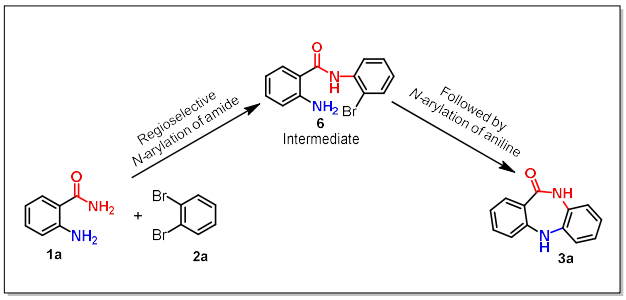


Scheme 2: Synthesis of Clozapine

Next, we turned our attention to the development of metal-catalyzed domino reaction that employs the use of 2-aminobenzamide and 2,3-dibromopyridine derivative. To our delight, 2-aminobenzamide (**1a**) and 2,3-dibromo-5-triflurometylpyridine (**2f**) were reacted successfully under the standard condition to obtain the only cyclized product benzopyridodiazepinone (**3f**) in 60% yield (Entry 6). Furthermore, the substrate scope was also extended to the electron-donating dihaloarene. Reaction of 2-aminobenzamide with 5,6-dibromobenzo[*d*][1,3]dioxole **2g** yielded cyclized product **3g** in 53% yield.

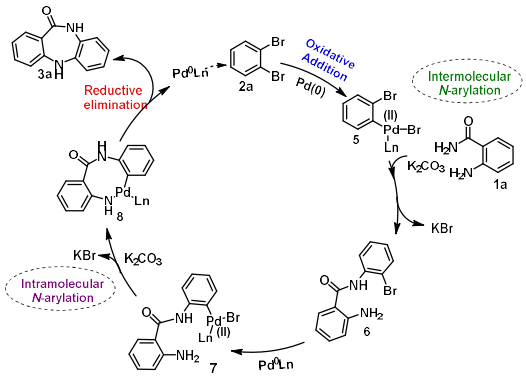
Subsequently, the translation application our current protocol was explored to the synthesis of an anti-psychotic drug, clozapine (Scheme 2). Importantly, known synthesis of dibenzodiazepinone moiety leading to the preparation of clozapine invariably involves multi-steps.[19] Reaction of 2-aminobenzamide and 1,2-dibromo-4-chlorobenzene under the optimized condition gave the desired dibenzodiazepinone **3e** regioselectivly in 70% yield.

The installation of *N*-methylpiperzine onto dibenzodiazepinone **3e** could be achieved using the known literature.[21]



Scheme 3: Possible domino route towards the synthesis of dibenzodiazepinone.

During optimization, a product corresponding to the regioselective *N*-arylation of amide group in 2-aminobenzamide was often obtained. Unlike the literature,[18] a control experiment using 2-aminobenzamide and bromobenzene under the optimized condition gave us 2-amino-*N*-phenylbenzamide confirming that *N*-arylation takes place at amide nitrogen. Based on this observation, the following domino reaction was proposed (Scheme 3).



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Scheme 4: Plausible mechanistic route for the synthesis of dibenzodiazepione

Finally, a plausible reaction mechanism is proposed in Scheme 4. In the first catalytic cycle, an oxidative addition of Pd^0 to the aryl halide would give **5**, which upon addition with 2-aminobenzamide in the presence of K_2CO_3 could give an intermediate **6**. In the second catalytic cycle, a palladium catalyzed intramolecular *N*-arylation of **7** to give **3a** is proposed. In this cycle, an oxidative addition of Pd^0 to the aryl halide would give **7** followed by **8**, which upon reductive elimination could yield **3a**.

Conclusion

In summary, we have developed domino reactions for the synthesis of dibenzodiazepinone by employing palladium-catalyzed double *N*-arylation reactions (inter and intra-molecular) starting from readily available 2-aminobenzamide and 1,2-dihaloarenes. This protocol was also extended to the synthesis of benzopyridodiazepinone by utilizing 2-aminobenzamide and 2,3-dihalopyridine derivatives. The domino approach was further utilized to the synthesis of a marketed anti-psychotic drug, clozapine. A key to the successful development of our protocol includes regioselective *N*-arylation of 2-aminobenzamide at amide nitrogen. Unlike the literature, the explanation for reverse regioselectivity observed in our case under palladium-catalysis requires further investigation.

Experimental Section

General Methods: All reagents and solvents were purchased from commercial sources and used as received. 1,2-Diamino(hetero)arenes and 1,2-dihalo(hetero)arenes were purchased from commercial vendors. All palladium-catalyzed domino reactions were degassed and performed in screw-capped vials under argon. The ^1H and ^{13}C NMR spectroscopic data were recorded with a 400 MHz spectrometer and are reported in δ units. The samples were dissolved in DMSO-d_6, and the coupling constants (*J* values) are reported in Hz. Column chromatography was performed on silica gel (100–200 or 230–400 mesh).

General Procedure for the Synthesis of Dibenzodiazepinones:

In a screw capped vial that was equipped with a rubber septum, a mixture of 2-aminobenzamide (0.5 mmol), 1,2 dibromobenzene (0.5 mmol), $Pd(OAc)_2$ (10 mol%), S-Phos (20 mol%), and K_2CO_3 (3 equiv) in toluene (1 mL) was purged with argon for approximately 10 min and then heated at 110 °C for 24 h under argon. The reaction mixture was cooled to room temperature and then diluted with an excess amount of ethyl acetate. The obtained suspension was filtered through a celite bed, and the filtrate was concentrated under reduced pressure.

2-amino-5-bromobenzamide (1b): In a screw capped reaction tube, a solution of 2-aminobenzamide (0.5 mmol) in acetonitrile (2 mL) and *N*-bromosuccinamide (0.6 mmol) was added and the reaction was heated at 60 °C for 10 min. Upon completion, the solution was diluted with EtOAc, and then washed by brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated to afford the desired substrate. The data of the substrate was confirmed by literature report.[22] White solid. ^1H NMR (400 MHz, DMSO-d_6): δ 7.89 (s, 1H), 7.73 (s, 1H), 7.26 – 7.24 (dd, *J* = 2.0, 8.76 Hz, 1H), 7.21 (s, 1H), 6.71 (s, 1H), 6.69 – 6.66 (d, 8.80 Hz, 2H).

2-(Methylamino)benzamide (1d): Synthesised according to general method mentioned in literature:[23] White solid. ^1H NMR (400 MHz, DMSO-d_6): δ 8.01 – 8.00 (d, *J* = 4.84 Hz, 1H), 7.81 (s, 1H), 7.60 – 7.58 (dd, *J* = 1.24, 7.84 Hz, 1H), 7.30 – 7.26 (t, *J* = 7.32 Hz, 1H), 7.15 (s, 1H), 6.62 – 6.60 (d, *J* = 8.36 Hz, 1H), 6.54 – 6.50 (t, *J* = 7.32 Hz, 1H), 2.77 – 2.76 (d, *J* = 5.08 Hz, 3H).

10,11-Dihydro-5*H*-dibenzo[*b,e*][1,4]diazepinones (3a):[24] White solid. ^1H NMR (400 MHz, DMSOd_6): δ 9.85 (s, 1H), 7.85 (s, 1H), 7.68 – 7.66 (dd, *J* = 1.04, 7.84 Hz, 1H), 7.35 – 7.31 (t, *J* = 7.04 Hz, 1H), 7.00 – 6.88 (m, 6H).

2-Bromo-5,10-dihydro-11*H*-dibenzo[*b,e*][1,4]diazepin-11-one (3b):[24] Yellow solid. ^1H NMR (400 MHz, DMSO-d_6): δ 9.98 (s, 1 H), 8.05 (s, 1H), 7.74 –7.73 (d, *J* = 2.52 Hz, 1H), 7.51 – 7.48 (dd, 2.56, 8.64 Hz, 1H), 6.97 – 6.93 (m, 5H).

2-Chloro-5, 10-dihydro-11*H*-dibenzo[*b,e*][1,4]diazepin- 11-one (3c):[24] Yellow solid. ^1H NMR (400 MHz, DMSOd_6): δ 10.00 (s, 1H), 8.05 (s, 1H), 7.62 – 7.61 (d, *J* = 2.6Hz, 1H), 7.40 – 7.37 (dd, *J* = 2.64, 8.64 Hz 1H), 7.02 – 6.94 (m, 5H).

5-Methyl-5,10-dihydro-11*H*-dibenzo[*b,e*][1,4]diazepin-11-one (3d): White solid. ^1H NMR (400 MHz, DMSO-d_6): δ 10.23 (s, 1H), 7.64 – 7.62 (d, *J* = 7.68 Hz, 1H), 7.51 – 7.46 (t, *J* = 8.36 Hz, 1H), 7.19 – 7.17 (d, *J* = 7.84 Hz, 2H), 7.10 – 7.04 (m, 4H), 3.26 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.0, 153.4, 145.0, 133.2, 131.4, 129.2, 127.3, 125.1, 124.33, 123.0, 121.7, 119.5, 118.0, 29.8. HRMS: calcd for $C_{14}H_{12}N_2O$ $[M+H]^+$ 225.1028, found 225.1000.

8-Chloro-5,10-dihydro-11*H*-dibenzo[*b,e*][1,4]diazepin-11-one (3e):[25] Brown solid. ^1H NMR (400 MHz, DMSO-d_6): δ 9.96 (s, 1H), 7.99 (s, 1H), 7.69 – 7.67 (d, *J* = 7.48 Hz, 1H), 7.36-7.35 (d, *J* = 5.32 Hz, 1H), 7.00 – 6.91 (m, 5H).

3-(Trifluoromethyl)-5,11-dihydro-6*H*-benzo[*e*]pyrido[3,2-*b*][1,4]diazepin-6-one (3f): Yellow solid. ^1H NMR (400 MHz, DMSOd_6): δ 10.03 (s, 1H), 9.21 (s, 1H), 8.23 (s, 1H), 7.77 – 7.75 (dd, *J* = 1.56, 7.92 Hz, 1H), 7.54 – 7.53 (s, *J* = 1.84 Hz, 1H), 7.42 – 7.38 (t, *J* = 8 Hz, 1H), 7.16 – 7.14 (d, *J* = 7.52 Hz, 1H), 6.97 – 6.94 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.0, 154.0, 145.6 140.0, 134.5, 132.8, 125.6, 124.47, 123.0, 122.0, 120.27, 119.71. HRMS: calcd for $C_{13}H_8F_3N_3O$ $[M+H]^+$ 280.0698, found 280.0679.

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5,11-dihydro-10H-[1,3]dioxolo[4',5':4,5]benzo[1,2-b]benzo[e][1,4]diazepin-10-one (3g): Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.65 (s, 1H), 7.64-7.62 (d, J = 7.72 Hz, 1H), 7.54 (s, 1H), 7.34 – 7.30 (m, 1H), 6.95 – 6.90 (m, 2H), 6.64 (s, 1H), 6.57 (s, 1H), 5.92 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.6, 151.8, 144.5, 143.5, 134.9, 133.4, 132.3, 123.8, 123.6, 121.4, 119.4, 102.7, 101.7, 101.4. HRMS: calcd for $C_{14}H_{10}N_2O_3$ $[M+H]^+$ 255.0770, found 255.0757.

2-amino-*N*-phenylbenzamide (3h):[23] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.60-7.58 (d, J = 7.84 Hz, 2H), 7.50 – 7.48 (dd, J = 1.24, 8.28 Hz, 1H), 7.41 – 7.37 (t, J = 8.08 Hz, 2H), 7.30 – 7.26 (m, 1H), 7.19 – 7.15 (t, J = 7.36 Hz, 1H), 6.75 – 6.72 (m, 2H), 5.51 (s, 1H).

2-Amino-*N*-(2-bromophenyl)benzamide (6):[17] White solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.75 (s, 1H), 7.75 – 7.71 (m, 2H), 7.57 – 7.54 (dd, J = 1.36, 7.88 Hz, 1H), 7.44 – 7.40 (m, 1H), 7.24 – 7.19 (m, 2H), 6.77 – 6.75 (d, J = 8.24 Hz, 1H), 6.61 – 6.57 (t,7.04 Hz, 1H), 6.46 (s, 2H).

Conflicts of interest

"There are no conflicts to declare".

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Palladium-catalysed regioselective *N*-arylation of anthranilamides: A tandem route for dibenzodiazepinone synthesis

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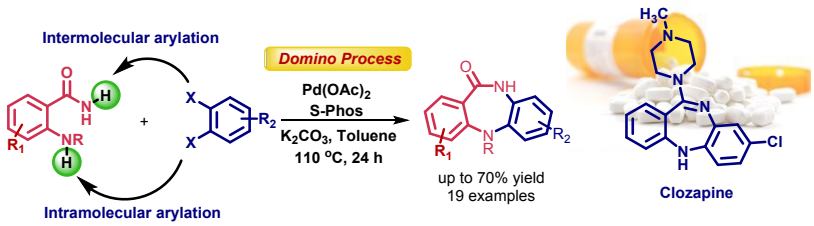

A palladium-catalyzed tandem reaction of 2-aminobenzamide and 1,2-dihaloarenes for the synthesis of dibenzodiazepinone via double *N*-arylations (inter and intra-molecular) has been achieved.