Palladium-catalyzed \( \text{N-Arylation of 1-substituted-1H-tetrazol-5-amines} \)

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**ABSTRACT**

A palladium-catalyzed \( \text{N-arylation of 1-substituted-1H-tetrazol-5-amines has been described for the first time. The reaction provides good yields of desired products with broad substrate scope and good functional group tolerance.} \)

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1. Introduction

Nitrogen-heterocyclic scaffolds are one of the most common structural motifs in pharmaceuticals [1]. As such 5-aminotetrazole is an important heterocyclic moiety of many bioactive compounds (Fig. 1). Substituted 5-aminotetrazoles exhibit versatile biological activities such as antiallergic [2], antiinflammatory [3], antidiabetic [4], antineoplastic [5] and antibiotic activity [6]. Moreover, 5-aminotetrazoles provide excellent inhibition against the corrosion of stainless steel [7] and are used as cholecystokinin B (CCK-B) receptor antagonists [8] and ligands in coordination chemistry [9]. Recent studies have described the use of 5-aminotetrazoles as photoprecursors of reactive intermediates [10].

Two main synthetic strategies for the synthesis of N5-substituted 5-aminotetrazoles are reported in the literature. The classical approach utilizes the formation of the tetrazole ring from \( \text{N-substituted acyclic precursors (Fig. 2) [11,12], and converse approach involves N5-amino group functionalization of the previously formed 5-aminotetrazoles [2,13,14].} \) Recently, Bolliokolla and co-workers developed copper-catalyzed double arylation of 5-aminotetrazoles for the synthesis of substituted 1-aryl-5-(N-arylamino)-tetrazoles [15].

Palladium-catalyzed arylation of amines has emerged as a powerful tool in organic synthesis and medicinal chemistry [16,17]. Of particular interest is palladium catalyzed arylation of primary amine derivatives of five- and six-membered heterocyclic compounds, which have been challenging substrates [18,19]. As we have recently demonstrated, electrostatic map potential of 5-aminotetrazoles shows that most of the electron density is located in the tetrazole ring while the amino group is in the blue region. This indicates that amino group is electron deficient and therefore less nucleophilic [20].

Herein, we report the first example of a palladium-catalyzed N-arylation of 1-substituted-1H-tetrazol-5-amines.

2. Results and discussion

In order to optimize the reaction condition, we began our study by choosing readily available 1-benzyl-1H-tetrazol-5-amine \( 1a \) and bromobenzene \( 2a \) as the model substrates with catalytic amount of \( \text{Pd}_2(\text{dba})_3 \) (10 mol % Pd with respect to \( 2a \)) as source of palladium and \( \text{NaO}^\text{-Et} \) (1.2 equiv) as a base, in toluene at 105 °C. An excess amount of the 5-aminotetrazole substrate was used in the reaction in order to prevent the formation of diarylated product. Using biaryl phosphane ligand JohnPhos (20 mol % with respect to \( 2a \)) the desired product \( 3a \) was obtained in 8% isolated yield after 24 h reaction time (Table 1, entry 1). Unfortunately, the reaction with \( \text{SPhos} \) was inefficient (Table 1, entry 2). When the
reaction was carried out in 1,4-dioxane as solvent using JohnPhos as ligand under the same conditions, 34% of 3a was isolated (Table 1, entry 3). To further improve the yield, different ligands were evaluated (Table 1, entries 4–6). With BrettPhos and t-BuXPhos significantly improved yields were observed (Table 1, entries 4 and 5). However, dppf was found to be unsuitable for the reaction (Table 1, entry 6). Moreover, shortening the reaction time from 24 h to 10 h was proven to be detrimental (Table 1, entry 7 vs entry 5). Notably, screening of the base revealed that K$_2$CO$_3$ was also very effective (Table 1, entry 8). On the other hand, Cs$_2$CO$_3$ was less effective in this reaction and resulted in lower yield (Table 1, entry 9).

Fig. 1. Important molecules containing 5-aminotetrazole moiety.

Fig. 2. Synthetic methods for the preparation of N-aryl 1-substituted-1H-tetrazol-5-amines.
With the optimized reaction conditions in hand, we examined the substrate scope with respect to arylbromides. As shown in Table 2, a series of arylbromides, including those with electron-donating group (–OMe) and others with electron-withdrawing groups (–NO2, –CN, –CO2Me, –CHO, and –COCH3) were transformed into the desired products in moderate to good yields (Table 2, 3b–3g), providing a potential point for further functionalization of the coupling products. In the cases of substrates with sensitive functional groups, K2CO3 was used as base (Table 2, 3d–3g). In addition, with 1-bromo-4-chlorobenzene and 1-bromo-3-chlorobenzene excellent selectivity was observed (Table 2, 3h and 3i). Moreover, when sterically demanding 2-bromo-5-chlorotoluene was employed as substrate, the reaction provided the corresponding product 3j in good yield. The scope of this method was further investigated by utilizing heteroaryl bromides. The present method is also applicable to 3-bromopyridine and corresponding product 3l was obtained in 51% yield, while there was no reaction with 2-bromothiophene (Tables 2, 3k). Notably, the reaction could be scaled up to 1 mmol scale, yielding 3a in 91% isolated yield.

Next, we examined the substrate scope with respect to 1-substituted-1H-tetrazol-5-amines and arylbromides. As shown in Table 2, a series of arylbromides, including those with electron-donating group (–OMe) and others with electron-withdrawing groups (–NO2, –CN, –CO2Me, –CHO, and –COCH3) were transformed into the desired products in moderate to good yields (Table 2, 3b–3g), providing a potential point for further functionalization of the coupling products. In the cases of substrates with sensitive functional groups, K2CO3 was used as base (Table 2, 3d–3g). In addition, with 1-bromo-4-chlorobenzene and 1-bromo-3-chlorobenzene excellent selectivity was observed (Table 2, 3h and 3i). Moreover, when sterically demanding 2-bromo-5-chlorotoluene was employed as substrate, the reaction provided the corresponding product 3j in good yield. The scope of this method was further investigated by utilizing heteroaryl bromides. The present method is also applicable to 3-bromopyridine and corresponding product 3l was obtained in 51% yield, while there was no reaction with 2-bromothiophene (Tables 2, 3k). Notably, the reaction could be scaled up to 1 mmol scale, yielding 3a in 91% isolated yield.

Table 1
Optimization of the palladium-catalyzed N-arylation reaction conditionsa.

| entry | ligand    | base    | solvent | time (h) | yield (%) b |
|-------|-----------|---------|---------|----------|-------------|
| 1     | JohnPhos  | NaOtt-Bu| PhMe    | 24       | 8           |
| 2     | SPhos     | NaOtt-Bu| PhMe    | 24       | –           |
| 3     | JohnPhos  | NaOtt-Bu| dioxane | 24       | 34          |
| 4     | BrettPhos | NaOtt-Bu| dioxane | 24       | 82          |
| 5     | t-BuXPhos | NaOtt-Bu| dioxane | 24       | 91          |
| 6     | dppf      | NaOtt-Bu| dioxane | 24       | 18          |
| 7     | t-BuXPhos | NaOtt-Bu| dioxane | 10       | 40          |
| 8     | t-BuXPhos | K2CO3   | dioxane | 24       | 90          |
| 9     | t-BuXPhos | Cs2CO3  | dioxane | 24       | 79          |

a Reactions were performed in a flame-dried closed reaction tube. Pd2(dba)3 (10 mol % Pd), ligand (20 mol %) and base (1.2 equiv) were added to the reaction tube followed by the solvent. The mixture was stirred under an inert atmosphere at room temperature for 5 min, after which 2a (1.0 equiv) and 1a (1.2 equiv) were added. The tube was sealed and the mixture was heated at 105 °C in an oil bath for the indicated reaction time.

b Isolated yield.

With the optimized reaction conditions in hand, we examined the substrate scope with respect to arylbromides. As shown in Table 2, a series of arylbromides, including those with electron-donating group (–OMe) and others with electron-withdrawing groups (–NO2, –CN, –CO2Me, –CHO, and –COCH3) were transformed into the desired products in moderate to good yields (Table 2, 3b–3g), providing a potential point for further functionalization of the coupling products. In the cases of substrates with sensitive functional groups, K2CO3 was used as base (Table 2, 3d–3g). In addition, with 1-bromo-4-chlorobenzene and 1-bromo-3-chlorobenzene excellent selectivity was observed (Table 2, 3h and 3i). Moreover, when sterically demanding 2-bromo-5-chlorotoluene was employed as substrate, the reaction provided the corresponding product 3j in good yield. The scope of this method was further investigated by utilizing heteroaryl bromides. The present method is also applicable to 3-bromopyridine and corresponding product 3l was obtained in 51% yield, while there was no reaction with 2-bromothiophene (Tables 2, 3k). Notably, the reaction could be scaled up to 1 mmol scale, yielding 3a in 91% isolated yield.

Next, we examined the substrate scope with respect to 1-substituted-1H-tetrazol-5-amines and arylbromides. As shown in Table 2, 1-(4-methoxybenzyl)-1H-tetrazol-5-amine 1b reacted smoothly with both electron-poor and electron-rich aryl bromides and afforded the corresponding desired substituted products 3m–3r in moderate to excellent yields (54–95%). In addition, 4-[(5-amino-1H-tetrazol-1-yl)methyl]benzonitrile 1c and 1-propyl-1H-tetrazol-5-amine 1d reacted with bromobenzene 2a affording 3s and 3t in moderate yields. Furthermore, 1-phenyl-1H-tetrazol-5-amine 1e was also reacted with 2a and gave the desired product 3u in 71% yield.

The reaction conditions also proved applicable to the coupling reaction of 1-benzyl-1H-tetrazol-5-amine 1a with iodobenzene 4 and chlorobenzene 5, and to a lesser extent to the coupling reaction of 1a and phenyl trifluoromethanesulfonate 6 (Scheme 1).

Finally, as an expansion of this study, we explored the removal of benzyl group [21] in order to obtain N-phenyl-1H-tetrazol-5-amine. Under hydrogen atmosphere (1 atm), 3a was converted into 7a in almost quantitative yield, using Pd/C (5 mol % Pd) as a catalyst (Scheme 2).

3. Conclusions
In conclusion, we have successfully developed an efficient palladium-catalyzed N-arylation of 1-substituted-1H-tetrazol-5-amines. The reaction exhibits broad substrate scope and good functional group compatibility. Considering the generality, this methodology could be of synthetic utility in the industry and drug discovery and development process.

4. Experimental section
4.1. General information
Unless stated otherwise, all solvents and reagents were obtained...
from commercial sources and used without further purification. Dry-flash chromatography was performed on silica gel (0.018–0.032 mm). Melting points were determined on a Boetius PMHK apparatus and are not corrected. IR spectra were recorded on a Thermo Scientific Nicolet 6700 FT-IR Diamond Crystal instrument. 1H and 13C NMR spectra were recorded on a Bruker Ultrashield Avance III spectrometer (at 500 and 125 MHz, respectively) using DMSO-<sup>d6</sup> (unless stated otherwise) as the solvent. Chemical shifts are expressed in parts per million (ppm) on the (δ) scale. Chemical shifts were calibrated relative to those of the solvent. All new compounds were analyzed by high resolution tandem mass spectrometry using LTQ Orbitrap XL (Thermo Fisher Scientific Inc., USA) mass spectrometer. The sample was dissolved in MeCN and it was injected directly. Ionization was done in positive mode on heated electrospray ionization (HESI) probe. HESI parameters were: spray voltage 4.7 kV, vaporizer temperature 60 °C, sheath and auxiliary gas flow 24 and 10 (arbitrary units), respectively, capillary voltage 49 V, capillary temperature 275 °C, tube lens voltage 80 V, resolution (at m/z 400): 30000.

4.2. Synthesis

Compounds 1-benzyl-1H-tetrazol-5-amine (1a) [22], 1-propyl-1H-tetrazol-5-amine (1d) [23] and 1-phenyl-1H-tetrazol-5-amine (1e) [24] were synthesized according to the previously reported procedures.

4.2.1. 1-(4-Methoxybenzyl)-1H-tetrazol-5-amine (1b) [19].

In a flame-dried flask, CNBr (811 mg, 7.7 mmol, 2 equiv) was dissolved in dry acetonitrile (13 mL) at 0 °C. NaOH (2.373 g, 36.5 mmol, 9.5 equiv) was added at the cooled solution and the resulting mixture was stirred at 0 °C for 4 h. The precipitate was filtered on a Hirsch funnel and the filtrate was added dropwise to a stirred emulsion of (4-methoxyphenyl)methanamine (500 µL,
Table 3
Substrate scope for palladium catalyzed $N$-arylation\textsuperscript{a,4}

| $1b$, $R_1$ | $1c$, $R_1$ | $1d$, $R_1$ | $1e$, $R_1$ |
|---|---|---|---|
| 4-OMePhCH$_2$- | 4-CNPhCH$_2$- | n-Pr | Ph |

\textsuperscript{a}Reactions conditions: 1 (0.300 mmol, 1.2 equiv), 2 (0.250 mmol, 1.0 equiv), Pd$_2$(dba)$_3$ (0.012 mmol, 10 mol $\%$ Pd), $t$-BuXPhos (0.050 mmol, 20 mol $\%$), NaO$t$-Bu (0.300 mmol, 1.2 equiv), 1,4-dioxane (1 mL), 105 $^\circ$C, 24 h, Ar. Isolated yields are shown.

\textsuperscript{b}Reactions conditions: 1 (0.180 mmol, 1.2 equiv), 2 (0.150 mmol, 1.0 equiv), Pd$_2$(dba)$_3$ (0.008 mmol, 10 mol $\%$ Pd), $t$-BuXPhos (0.030 mmol, 20 mol $\%$), K$_2$CO$_3$ (0.180 mmol, 1.2 equiv), 1,4-dioxane (1.9 mL), 105 $^\circ$C, 24 h, Ar. Isolated yields are shown.

Scheme 1. Reaction of 1-benzyl-1H-tetrazol-5-amine $1a$ with iodobenzene $4$, chlorobenzene $5$ and phenyl trifluoromethanesulfonate $6$. 
3.8 mmol) in water (4 mL) at 0 °C. The resulting mixture was stirred at room temperature for 48 h. After the time has passed, the solvents were removed under the reduced pressure. The remaining residue was filtered and washed with water and acetonitrile. The product was dried under reduced pressure to afford 1-(4-

[571 mg, 73%]; m.p. 183 ◦C). The residue was washed with water (30 mL), brine (30 mL) and the organic solution was dried over anhydrous MgSO4. The mixture was filtered and the solvents were removed under the reduced pressure. The crude product was purified by dry-flash column chromatography on SiO2.

4.2.5.2. Reaction of 1-benzyl-1H-tetrazol-5-amine (1c)

Following the general procedure A for palladium catalyzed arylation, compound 1c was obtained after dry-flash column chromatography (SiO2: Hex/EtOAc = 7/3) as a pale yellow solid (228 mg, 91%) from 210 mg (1.2 mmol) of 1a; m.p. 165–168 °C. IR (ATR) = 3729, 3276, 3209, 3129, 3061, 2925, 2854, 1615, 1577, 1540, 1498, 1457, 1332, 1104, 748, 716, 692 cm−1. 1H NMR (500 Hz, DMSO-d6): δ 9.46 (s, 1H), 7.65–7.60 (m, 2H), 7.38–7.30 (m, 5H), 7.26–7.22 (m, 2H), 7.02–6.96 (m, 1H), 5.64 (s, 2H). 13C{1H} NMR (125 Hz, DMSO-d6): δ 152.5, 139.8, 135.2, 129.0, 128.9, 128.1, 127.4, 122.0, 117.6, 48.2 ppm. HRMS (ESI/Orbitrap) m/z: [M + H]+ Calcd for Cu4H14N5 252.12492; Found 252.12377.

4.2.5.1. Reaction of 1-benzyl-1H-tetrazol-5-amine 1a and iodo-benzene 4.

Following the general procedure A for palladium catalyzed arylation, compound 3a was obtained after dry-flash column chromatography (SiO2: Hex/EtOAc = 7/3) as a pale yellow solid (12 mg, 68%) from 1a (15 mg, 0.086 mmol) and iodo-benzene 4 (8 µL, 0.071 mmol).

4.2.5.3. Reaction of 1-benzyl-1H-tetrazol-5-amine 1a and phenyl trifluoromethanesulfonate 6.

Following the general procedure A for palladium catalyzed arylation, compound 3a was obtained after dry-flash column chromatography (SiO2: Hex/EtOAc = 7/3) as a pale yellow solid (5 mg, 28%) from 1a (15 mg, 0.086 mmol) and phenyl trifluoromethanesulfonate 6 (16 mg, 0.071 mmol).

4.2.6. 1-Benzyl-N-(4-methoxyphenyl)-1H-tetrazol-5-amine (3b)

Following the general procedure A for palladium catalyzed arylation, compound 3b was obtained after dry-flash column chromatography (SiO2: Hex/EtOAc = 7/3) as a pale orange solid (50 mg, 71%); m.p. 137–139 °C. IR (ATR) = 3317, 3032, 2929, 1634, 1607, 1562, 1512, 1458, 1243, 1033 cm−1. 1H NMR (500 Hz, DMSO-d6): δ 9.26 (s, 1H), 7.54 (d, J = 9.0 Hz, 2H), 7.40–7.35 (m, 2H), 7.34–7.30 (m, 1H), 7.27–7.22 (m, 2H), 6.93 (d, J = 9.0 Hz, 2H), 5.60 (s, 2H), 3.72 (s, 3H). 13C{1H} NMR (125 Hz, DMSO-d6): δ 155.7, 140.9, 132.7, 128.3, 118.5, 110.8, 47.1. HRMS (ESI/Orbitrap) m/z: [M + Na]1+ Calcd for C19H17N6O2Na 326.11408; Found 326.11344.
1.2. 1-Benzyl-N-(4-nitrophenoxy)-1H-tetrazol-5-amine (3e)

Following the general procedure B for palladium catalyzed arylation, compound 3e was obtained after dry-column chromatography (SiO$_2$: Hex/EtOAc = 8/2) as a yellow solid (57 mg, 70%); m.p. 139.8, 139.5, 135.7, 135.0, 128.9, 128.6, 128.2, 127.5, 117.0, 48.6. IR spectra (ATR) 3271, 3198, 3061, 2924, 1620, 1581, 1539, 1334, 1169, 834 cm$^{-1}$.

1H NMR (500 Hz, DMSO-$d_6$): $\delta$ 9.72 (s, 1H), 7.85–7.80 (m, 2H), 7.57–7.54 (m, 1H), 7.39–7.35 (m, 3H), 7.35–7.30 (m, 1H), 7.26–7.22 (m, 2H), 5.64 (s, 2H), 1.38 (s, 3H). HRMS (HESI/Orbitrap) m/z: [M + H]$^+$ Calcd for C$_{15}$H$_{16}$N$_5$O$_2$ 282.13549; Found 282.13465.

13C{1H} NMR (125 Hz, DMSO-$d_6$): $\delta$ 152.1, 141.2, 135.0, 133.4, 130.7, 128.8, 128.1, 127.4, 121.7, 116.9, 116.1, 48.3. HRMS (HESI/Orbitrap) m/z: [M + H]$^+$ Calcd for C$_{15}$H$_{13}$N$_6$O$_2$ 297.10999; Found 297.10881.

4.2. 1-Benzyl-N-(3-chlorophenyl)-1H-tetrazol-5-amine (3i)

Following the general procedure A for palladium catalyzed arylation, compound 3i was obtained after dry-column chromatography (SiO$_2$: Hex/EtOAc = 7/3) as a yellow solid (42 mg, 58%); m.p. 173–176 °C IR (ATR): 3256, 3189, 3105, 3059, 1618, 1572, 1517, 1477, 1455, 1389, 1329, 1112, 785, 723 cm$^{-1}$. 1H NMR (500 Hz, DMSO-$d_6$): $\delta$ 9.72 (s, 1H), 7.85–7.80 (m, 2H), 7.57–7.54 (m, 1H), 7.39–7.35 (m, 3H), 7.35–7.30 (m, 1H), 7.26–7.22 (m, 2H), 7.03–7.06 (m, 1H), 5.64 (s, 2H), 1.38 (s, 3H). HRMS (HESI/Orbitrap) m/z: [M + H]$^+$ Calcd for C$_{15}$H$_{16}$N$_5$O$_2$ 282.13549; Found 282.13465.

13C{1H} NMR (125 Hz, DMSO-$d_6$): $\delta$ 152.1, 141.2, 135.0, 133.4, 130.7, 128.8, 128.1, 127.4, 121.7, 116.9, 116.1, 48.3. HRMS (HESI/Orbitrap) m/z: [M + H]$^+$ Calcd for C$_{15}$H$_{13}$N$_6$O$_2$ 297.10999; Found 297.10881.

4.2.1.e. N-(1-Benzyl-1H-tetrazol-5-yl)pyridin-3-amine (3j)

Following the general procedure A for palladium catalyzed arylation, compound 3j was obtained after dry-column chromatography (SiO$_2$: Hex/EtOAc = 7/3) as a pink solid (32 mg, 49%); m.p. 161.7–162 °C IR (ATR): 3268, 3210, 3112, 3065, 2956, 2923, 2227, 1611, 1566, 1509, 1334, 844 cm$^{-1}$.

1H NMR (500 Hz, DMSO-$d_6$): $\delta$ 10.07 (s, 1H), 7.27–7.24 (m, 2H), 5.67 (s, 2H), 1.38 (s, 3H). HRMS (HESI/Orbitrap) m/z: [M + H]$^+$ Calcd for C$_{15}$H$_{16}$N$_5$O$_2$ 282.13465; Found 282.13469.

13C{1H} NMR (125 Hz, DMSO-$d_6$): $\delta$ 151.8, 144.0, 134.9, 133.6, 128.9, 128.2, 127.4, 119.2, 117.5, 103.4, 48.5. HRMS (HESI/Orbitrap) m/z: [M + H]$^+$ Calcd for C$_{15}$H$_{15}$N$_6$O$_2$ 282.13040; Found 282.13040.
Following the general procedure A for palladium catalyzed arylation, compound 3n was obtained after dry-flash column chromatography (SiO2: Hex/EtOAc = 6/4) as a pale yellow solid (54 mg, 70%); m.p. 132–135 °C. IR (ATR) = 3266, 2956, 2930, 1612, 1582, 1535, 1513, 1462, 1249, 1179, 1034 cm−1. 1H NMR (500 Hz, DMSO-d6): δ 2.92 (s, 2H), 7.60–7.50 (m, 2H), 7.25–7.20 (m, 2H), 6.95–6.90 (m, 4H), 5.50 (s, 2H), 3.72 (s, 3H), 3.71 (s, 3H). 13C{1H} NMR (125 Hz, DMSO-d6): δ 159.0, 154.6, 152.6, 133.0, 129.1, 127.0, 119.5, 114.2, 55.2, 55.1, 47.6. HRMS (HESI/Orbitrap) m/z: [M + H]+ Calcd for C15H14ClN5O3 338.0768; Found 338.0765.

Following the general procedure A for palladium catalyzed arylation, compound 3o was obtained after dry-flash column chromatography (SiO2: Hex/EtOAc = 6/4) as a pale yellow solid (58 mg, 71%); m.p. 171–173 °C. IR (ATR) = 3264, 3102, 3072, 2960, 1620, 1583, 1542, 1517, 1362, 1111, 821 cm−1. 1H NMR (500 Hz, DMSO-d6): δ 10.27 (s, 1H), 8.26 (d, J = 9.0 Hz, 2H), 7.86 (d, J = 9.0 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 6.92 (d, J = 8.5 Hz, 2H), 5.60 (s, 2H), 3.71 (s, 3H). 13C{1H} NMR (125 Hz, DMSO-d6): δ 159.2, 151.4, 146.0, 141.1, 129.2, 126.6, 125.4, 117.0, 114.2, 55.1, 48.2. HRMS (HESI/Orbitrap) m/z: [M + Na]+ Calcd for C15H16N5ONa 349.0521; Found 349.10096.

Following the general procedure A for palladium catalyzed arylation, compound 3p was obtained after dry-flash column chromatography (SiO2: Hex/EtOAc = 7/3) as an orange solid (52 mg, 66%); m.p. 198–200 °C. IR (ATR) = 3265, 3198, 3119, 3060, 1614, 1570, 1514, 1490, 1458, 1263, 1252, 821 cm−1. 1H NMR (500 Hz, DMSO-d6): δ 9.60 (s, 1H), 7.68 (d, J = 9.0 Hz, 2H), 7.39 (d, J = 9.0 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H), 6.92 (d, J = 8.5 Hz, 2H), 5.54 (s, 2H), 3.71 (s, 3H). 13C{1H} NMR (125 Hz, DMSO-d6): δ 159.1, 152.0, 138.8, 129.2, 128.8, 126.9, 125.5, 119.1, 114.2, 55.1, 47.8. HRMS (HESI/Orbitrap) m/z: [M + Na]+ Calcd for C15H15ClN5O 338.0784; Found 338.07687.

Following the general procedure A for palladium catalyzed arylation, compound 3q was obtained after dry-flash column chromatography (SiO2: Hex/EtOAc = 7/3) as a yellow solid (43 mg, 54%); m.p. 173–174 °C. IR (ATR) = 3266, 3195, 3116, 3063, 2997, 2927, 1617, 1568, 1540, 1459, 1310, 1261, 780 cm−1. 1H NMR (500 Hz, DMSO-d6): δ 9.68 (s, 1H), 7.79–7.78 (m, 1H), 7.60–7.50 (m, 1H, 7.40–7.35 (m, 1H), 7.24 (d, J = 8.5 Hz, 2H), 7.05–7.00 (m, 1H), 6.92 (d, J = 8.5 Hz, 2H), 5.55 (s, 2H), 3.71 (s, 3H). 13C{1H} NMR (125 Hz, DMSO-d6): δ 159.1, 151.8, 141.2, 133.4, 130.7, 129.2, 126.8, 121.5, 116.9, 116.0, 114.2, 55.1, 47.9. HRMS (HESI/Orbitrap) m/z: [M + Na]+ Calcd for C15H14ClN5O 338.0784; Found 338.07730.

Following the general procedure A for palladium catalyzed arylation, compound 3r was obtained after dry-flash column chromatography (SiO2: Hex/EtOAc = 8/2) as a yellow viscous oil (58 mg, 71%); IR (ATR) = 3237, 2962, 1612, 1590, 1516, 1488, 1253, 1162, 819 cm−1. 1H NMR (500 Hz, DMSO-d6): δ 8.61 (s, 1H), 7.47–7.41 (m, 1H), 7.33–7.28 (m, 1H), 7.26–7.20 (m, 3H), 6.90–6.95 (m, 2H), 5.50 (s, 2H), 3.72 (s, 3H), 2.09 (s, 3H). 13C{1H} NMR (125 Hz, DMSO-d6): δ 159.1, 153.3, 136.8, 133.3, 130.2, 129.2, 128.4, 126.7, 126.3, 124.6, 114.2, 55.1, 48.0, 17.4. HRMS (HESI/Orbitrap) m/z: [M + H]+ Calcd for C16H17ClN6O 330.1126; Found 330.1145.
Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jorganchem.2018.11.007.

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