Optimization of the Suzuki Coupling Reaction in the Synthesis of 2-[(2-Substituted)phenyl]pyrrole Derivatives

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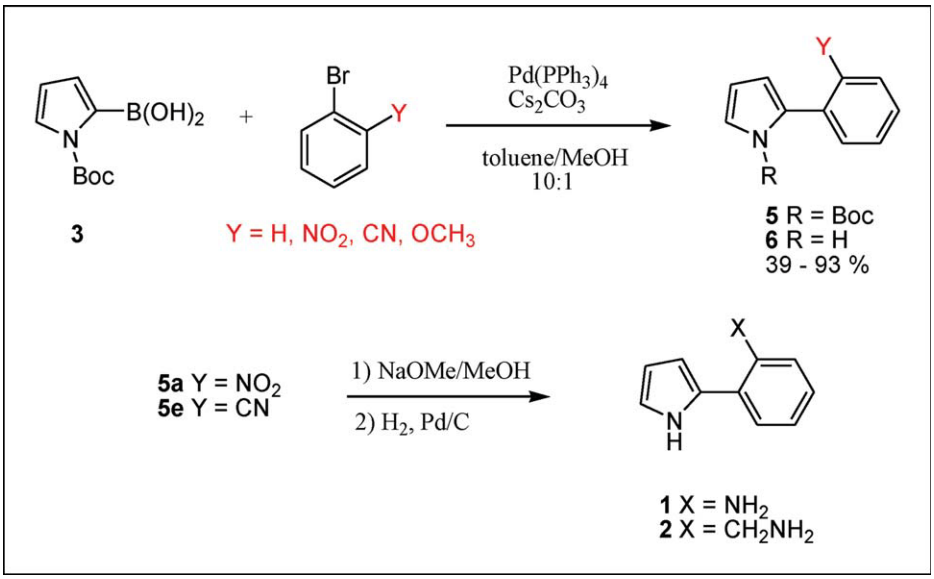

A facile three-step synthesis of 2-(2-aminophenyl)pyrrole (**1**) and 2-[(2-aminomethyl)phenyl]pyrrole (**2**) is reported by use of Suzuki coupling of *N*-Boc-pyrrol-2-yl boronic acid (**3**) and o-substituted aryl halogenides, followed by hydrogenation. The Pd-catalyzed cross-coupling reaction is optimized to be applicable to a wide range of substitued aryl halogenides, with electron-donating and electron-withdrawing substituents, **5a**–**g**. Moreover, Pd-catalyzed coupling of *o*-bromoaniline and **3** could be applied for the one-step preparation of pyrrolo[1,2-*c*]quinazolin-5(6*H*)-one (**8**).

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INTRODUCTION

The on-going project in our laboratory on adamantane-dipyrromethane anion receptors A and B [1,2] envisaged new host molecules in which hydrogen at the position 2 of the pyrrole ring is replaced by an aryl substituent bearing a hydrogen donor site in the ortho position. In particular, amino or methylamino groups, as in pyrrole derivatives **1** and **2**, are potentially good H-bond donors (Fig. 1).

Synthesis of pyrrole derivatives having molecular skeletons similar to **1** and **2** has been reported [3–8]. However, the synthetic strategy was mostly based on tedious multistep synthetic procedures involving a condensation of the pyrrole ring [3–8]. Recently, the one-pot synthesis of diverse 2-substituted, 2,3- and 2,5-disubstituted *NH*- and *N*-vinylpyrroles through the Trofimov reaction of ketoximes with acetylenes was reported [9]. This simple and efficient route to pyrrole derivatives is widely used [10].

On the other hand, modern synthetic methods more often rely on the versatile use of Pd-catalyzed C—C bond formation [11–16]. Thus, arylpyrroles can be prepared by Stille coupling of N-protected pyrrole stanannes with arylhalogenides [17], Suzuki–Miyaura coupling [18,19] of N-protected pyrrole boronic acid with arylhalogenides [20] as well as from N-protected pyrrole bromides with aryl boronic acids [21,22], or palladium-catalyzed direct arylation [23,24]. However, the arylation by o-substituted aryl halogenides often fails or proceeds with very low yield [20,25]. These reactions with sterically hindered reagents are possible but often employ modified Pd-catalyzed systems wherein structurally modified ligands are used [26].

Herein, we describe a facile three-step synthetic protocol for the preparation of pyrrole derivatives **1** and **2** that involves Suzuki coupling of the N-protected pyrrole boronic acid and nitrophenyl or cyanophenyl derivative, and subsequent hydrogenation to the amines. Also,

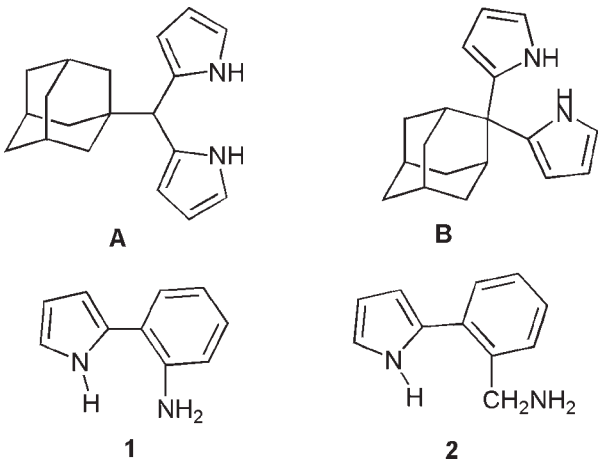


Figure 1. Structure of adamantane-dipyrromethanes **A** and **B** and pyrrole derivatives **1** and **2**.

keeping in mind the easy availability of the reagents used in the synthesis, particularly inexpensive commercial catalysts and ligands, the conditions for the Suzuki coupling were optimized.

RESULTS AND DISCUSSION

It is known that Pd-catalyzed reactions with *o*-bromoaniline are quite difficult as the amino group electronically deactivates the C—Br bond in the oxidative addition to the Pd catalyst [27,28]. Nevertheless, there are examples of direct Suzuki coupling for preparation of biaryls and heteroaryls involving an unprotected NH_2 group [29–35]. However, to the best of our knowledge, an attempt to couple a pyrrole moiety to o-substituted anilines in a Pd-catalyzed reaction has not been reported.

To avoid additional protection and deprotection steps of the amino group, we turned our attention to the Pd-catalyzed coupling reaction between *N*-Boc-pyrrol-2-yl boronic acid [36] and the aryl halogenide bearing ortho substituents that could be subsequently transformed to the amino group. Hence, for the synthesis of 2-(*o*-aminophenyl)pyrrole (**1**), first we performed the coupling reaction between *N*-Boc-pyrrol-2-yl boronic acid (**3**) and 2-nitrobromobenzene (**4a**, Scheme 1). We applied the protocol published by Burgess and co-workers [21,22] that includes $Pd(PPh_3)_4$ as a catalyst and an aqueous solution of Na_2CO_3 in a 5:1 mixture of toluene and methanol. However, under these conditions we obtained less than 2% of *N*-Boc-2-(*o*-nitrophenyl)pyrrole (**5a**) (Table 1, entry 1). The low yield prompted us to investigate the reaction conditions in more detail. To optimize the reaction conditions, various factors were investigated including catalyst (type and amount), base, solvent, and reaction time. The results are summarized in Table 1.

As the first reaction conditions did not work in our case, we removed water from the reaction mixture. Addition of solid Na_2CO_3 increased the yield, and the product **5a** was isolated in 26% yield (Table 1, entry 2). Changing the base to Cs_2CO_3 increased the yield of the product to 42%, but the product was isolated as the unprotected form of **5a** (Table 1, entry 3). Performing the reaction with a smaller amount of methanol was a disappointment even with prolonging the reaction time (Table 1, entry 4). The yield was also poor when solely toluene was used as a solvent (Table 1, entry 5). Similarly poor yields were obtained when dimethoxyethane (DME) was used as a solvent with either of the bases Na_2CO_3 or Cs_2CO_3 (Table 1, entries 6 and 7).

In all of the coupling reactions that proceeded with moderate yield of the product **5a**, the by-products **6a** and **7** [20] were also formed. Compound **6a** is the result of deprotection of **5a** in basic reaction conditions, and compound **7** is the product of a competitive homocoupling reaction that uses up the starting boronic acid **3**. To minimize the formation of by-product **7**, we examined the influence of the addition time of **3** to the reaction mixture.

Surprisingly, when the reaction was carried out in a 10:1 mixture of toluene:methanol and starting compound **3** was added to the reaction mixture dropwise, the yield of the coupling products was dramatically increased to 81% and the by-product **7** was formed in 2% yield (Table 1, entry 11). A similar result was obtained when the

Scheme 1

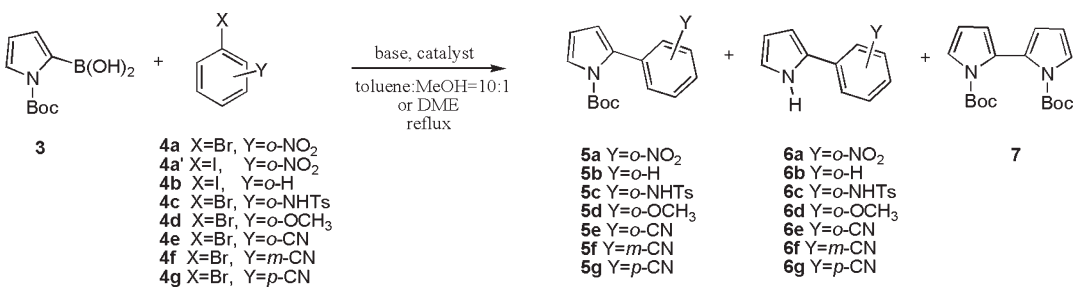


Table 1

Optimization of coupling reaction between pyrrole derivative **3** and *o*-nitroaryl halogenides **4a** and **4a′**.

Entry	Aryl	Catalyst (mol %)	Solvent[a]	Base	Time (h)[b]	Yield of coupling reaction (%)[c] (**5a** + **6a**)[d]	Yield, **7** (%)[c]
1	**4a**	$Pd(PPh_3)_4$ (5)	T:M (5:1)	Na_2CO_3 (aq)	0/48	2 (2 + 0)	–
2	**4a**	$Pd(PPh_3)_4$ (5)	T:M (5:1)	Na_2CO_3	0/48	26 (26 + 0)	11
3	**4a**	$Pd(PPh_3)_4$ (5)	T:M (5:1)	Cs_2CO_3	0/24	42 (0 + 42)	57
4	**4a**	$Pd(PPh_3)_4$ (5)	T:M (10:1)	Cs_2CO_3	0/32	24 (16 + 8)	30
5	**4a**	$Pd(PPh_3)_4$ (5)	T	Cs_2CO_3	0/24	11 (9+2)	30
6	**4a**	$Pd(PPh_3)_4$ (5)	DME	Na_2CO_3	0/24	36 (32+4)	5
7	**4a**	$Pd(PPh_3)_4$ (5)	DME	Cs_2CO_3	0/24	11 (9 + 2)	38
8	**4a**	$Pd(PPh_3)_4$ (5)	DME	Na_2CO_3	7/24	<2 (2 + 0)	1
9	**4a**	$Pd(PPh_3)_4$ (5)	DME	Cs_2CO_3	7/24	69 (64 + 5)	1
10	**4a**	$Pd(PPh_3)_4$ (5)	T:M (10:1)	Na_2CO_3	7/24	18 (15 + 3)	–
11	**4a**	$Pd(PPh_3)_4$ (5)	T:M (10:1)	Cs_2CO_3	7/24	81 (78 + 3)	2
12	**4a**	$Pd(PPh_3)_2Cl_2$ (5)	DME	Na_2CO_3	7/24	<2 (2 +0)	–
13	**4a**	$Pd(PPh_3)_2Cl_2$ (5)	DME	Cs_2CO_3	7/24	7 (7 + 0)	2
14	**4a**	$Pd(PPh_3)_2Cl_2$ (5)	T:M (10:1)	Na_2CO_3	7/24	61 (56 + 5)	3
15	**4a**	$Pd(PPh_3)_2Cl_2$ (5)	T:M (10:1)	Cs_2CO_3	7/24	28 (28 + 0)	3
16	**4a**	$Pd(PPh_3)_4$ (5)	T:M (10:1)	K_3PO_4	7/24	54 (52 + 5)	1
17	**4a**	$Pd(PPh_3)_4$ (5)	T:M (10:1)	$Ba(OH)_2$	7/24	<2 (2 + 0)	–
18	**4a**	$Pd(PPh_3)_4$ (2.5)	T:M (10:1)	Cs_2CO_3	7/24	67 (59 + 8)	1
19	**4a**	$Pd(PPh_3)_4$ (7.5)	T:M (10:1)	Cs_2CO_3	7/24	64 (45 + 19)	1
20	**4a′**	$Pd(PPh_3)_4$ (5)	T:M (10:1)	Cs_2CO_3	7/24	74 (68 + 6)	1
21	**4a′**	$Pd(PPh_3)_4$ (5)	DME	Cs_2CO_3	7/24	69 (67 + 2)	–

[a] T:M = toluene:MeOH; DME = dimethoxyethane.
[b] Time of the addition of **3**/overall reaction time.
[c] Isolated yield after chromatography.
[d] Ratio between **5a** and **6a** varies from run to run.

reaction was carried out in DME and by prolonging the addition time of **3**, formation of **7** can be kept below 5%.

We also explored the use of two palladium catalysts, $Pd(PPh_3)_4$ and $Pd(PPh_3)_2Cl_2$, in various solvents and with different bases. Experiments in DME (entries 12 and 13, Table 1), carried out with $Pd(PPh_3)_2Cl_2$ and bases Na_2CO_3 or Cs_2CO_3, gave **5a** in very low yields compared to reactions performed in a 10:1 mixture of toluene:methanol, which gave **5a** in moderate yields of 56% and 28% (entries 14 and 15). It is obvious that $Pd(PPh_3)_4$ acts as a more efficient catalyst than $Pd(PPh_3)_2Cl_2$ yielding products **5a** and **6a** in up to 81% yield. By varying the amount of Pd catalyst (entries 18 and 19), we found that both decrease or increase of the amount of catalyst gives rise to a decrease in the yield of **5a** and an increase in the yield of the unprotected derivative **6a**. Thus, the best yield of **5a** (78%) was achieved by the use of 5 mol % of $Pd(PPh_3)_4$, a 10:1 mixture of toluene and methanol and Cs_2CO_3 as a base (entry 11).

To probe for the influence of the base on the course of the reaction, we used K_3PO_4 and $Ba(OH)_2$ in addition to Na_2CO_3 and Cs_2CO_3. When K_3PO_4 was applied as a base (entry 16), the yield of the **5a** slightly decreased compared with the experiment done with Cs_2CO_3 (entry 11). The use of $Ba(OH)_2$ afforded **5a** in less than 2% yield (entry 17). The poor yield with $Ba(OH)_2$ could be explained by the problems that occurred during the work-up of the reaction. Fine colloidal particles of the base precipitated and caused a troublesome extraction of the product. Interestingly, in the presence of $Pd(PPh_3)_4$ as a catalyst, Cs_2CO_3 acted as a more efficient base than Na_2CO_3, yielding product **5a** in better yields in both sets of solvents. One of the reasons for a more pronounced effectiveness of Cs_2CO_3 over other bases could be due to an increased solubility of cesium carbonate in organic solvent such as methanol [37].

The change to a different halogen atom did not appear to have any significant effect on the course of the reaction. When *o*-nitroaryl iodide (**4a′**) was used under the same conditions, coupling products were obtained in a fairly analogous yield of 74% (Table 1, entry 20). Likewise, the change of the solvent to DME furnished **5a** in a similar yield (Table 1, entry 21).

After the examination of these various reaction parameters (catalyst, base, solvent, and reaction time), the optimal conditions were identified for the cross-coupling reaction of **3** and *o*-nitroaryl halogenides. These conditions were then applied to several o-substituted aryl

Table 2

Coupling reaction of **3** and arylhalogenides **4a–4g** in the presence of Cs_2CO_3 and $Pd(PPh_3)_4$.

Entry	Aryl	Solvent[a]	Yield of coupling reaction (%)[b] (**5a–5g** + **6a–6g**)[c]	Yield, **7** (%)[b]
1	**4a**	T:M (10:1)	81 (78 + 3)	2.5
2	**4a**	DME	69 (64 + 5)	1[d]
3	**4b**	T:M (10:1)	93 (86 + 7)	–
4	**4c**	T:M (10:1)	– (–)	–
5[e]	**4c**	T:M (10:1)	10 (10 + 0)	48
6	**4c**	DME	5 (5 + 0)	21
7	**4d**	T:M (10:1)	39 (39 + 0)	<1[d]
8	**4d**	DME	41 (41 + 0)	1[d]
9	**4e**	T:M (10:1)	61 (50 + 11)	–
10	**4e**	DME	32 (32 + 0)	8
11	**4f**	T:M (10:1)	32 (32 + 0)	–
12	**4g**	T:M (10:1)	51 (51+ 0)	–

[a] T:M = toluene:MeOH; DME = dimethoxyethane.
[b] Isolated yield after chromatography.
[c] Ratio between **5a–5g** and **6a–6g** varies from run to run.
[d] ^{1}H-NMR yield of the crude mixture, done by internal standard.
[e] Na_2CO_3 was used as a base.

halogenides **4a–4g** to investigate the scope of the reaction. The results of the cross-coupling reaction between **3** and various aryl halogenides are presented in Table 2. Again, in addition to the *N*-Boc-2-arylpyrroles **5a–5g**, unprotected arylpyrroles **6a–6g** and by-product **7** were formed. In all the reactions, performed in either 10:1 toluene:methanol mixture or DME, the highest yields were obtained when $Pd(PPh_3)_4$ was used as a catalyst, Cs_2CO_3 as a base, and the *N*-Boc-pyrrole boronic acid was added to the reaction mixture in small portions during **7h** and with subsequent heating for 17 h. It is noteworthy to mention that the crucial parameter for a successful reaction is the portionwise addition of **3** to the reaction mixture. As can be seen from Table 2, the best yield of **5** was obtained with iodobenzene, which gave more than 93% of coupled 2-phenylpyrrole (**5b** + **6b**).

When aryl halogenide with a tosyl-protected amino group was subjected to the reaction, the results were disappointing because there was no isolable product (Table 2, entry 4). However, the reaction with Na_2CO_3 as a base gave 10% of **5c** and 48% of the by-product **7** (Table 2, entry 5). It is possible that the *p*-toluenesulfonyl group which is sterically congested, deactivates the C—Br bond toward the oxidative addition to the Pd catalyst, and thus, a competitive reaction of homocoupling takes place to a greater extent.

The coupling reaction with the substrate **4d** bearing an electron-donating methoxy group at the ortho position furnished **5d** [22] in moderate yields (Table 2, entries 7 and 8). The reaction with 2-bromobenzonitrile (**4e**) was more successful when carried out in a 10:1 mixture of toluene and methanol than in DME (Table 2, entries 9 and 10). Reactions carried out with *meta*- and *para*-substituted nitriles **4f** and **4g** gave coupling products similar to the reaction with *ortho*-nitrile.

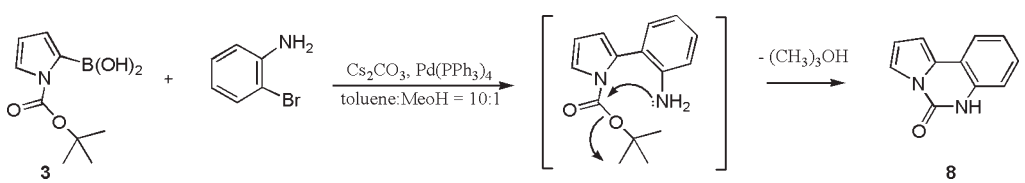
As shown in Tables 1 and 2, the coupling reaction is efficient with aryl bromides substituted by electron-withdrawing groups such as nitro and cyano. The best result was achieved with the *o*-nitrobromobenzene and this is in accordance with the proposition of Widdowson and Wilhelm [38] that a nitro group in the 2-position may coordinate an incoming Pd atom, and thus, help in the insertion step of the catalytic cycle.

Good results for Suzuki coupling reactions between pyrrole boronic acid derivative **3** and ortho-substituted arylhalogenides prompted us to test if *o*-bromoaniline as a substrate would undergo the desired coupling reactions. Indeed, using the above optimized reaction conditions, we obtained the coupling product in 23% yield, but in addition some secondary cyclization took place. Namely, after the first Pd-catalyzed coupling step, ring closure occurs due to a nucleophilic attack of the aniline amino-group on the carbonyl of the Boc-protecting group (Scheme 2).

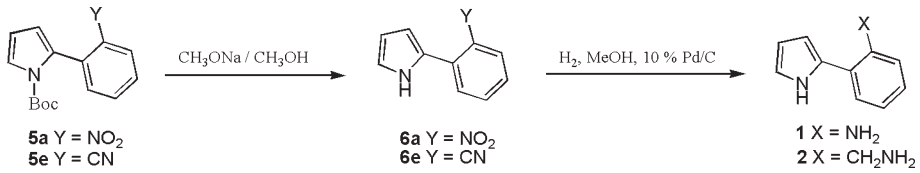
Obtained derivative **8** has a quinazoline skeleton which is in focus of interest in medicinal chemistry because of its very pronounced biological activities such as antiviral, antimalarial, antibacterial, and antihypertensive [39]. Therefore, this type of reaction could be of great importance for obtaining quinazoline derivatives in contrast to multistep synthesis employed to date in the literature [40].

Preparation of the title compounds, amino-derivatives **1** and **2**, was straightforward from nitro- and cyanoarylpyrroles **5a** and **5e**, respectively, as shown in Scheme 3. Removal of the Boc-protecting group was performed by sodium methoxide in methanol. The proceeding catalytic reduction of the nitro- and cyano-derivatives **6a** and **6e** was accomplished by hydrogenation in methanol over the inexpensive catalyst 10% Pd-C, giving amino derivatives **1** [41] and **2** in 63% and 58% yield, respectively.

Scheme 2



Scheme 3



5a Y = NO_2
5e Y = CN

6a Y = NO_2
6e Y = CN

1 X = NH_2
2 X = CH_2NH_2

In the catalytic reduction of **6e**, besides the amino product **2**, a small amount of 2-(*o*-methylphenyl)pyrrole (**9**) [42] was also formed.

CONCLUSIONS

We have found a good synthetic protocol for the preparation of 2-(2-aminophenyl)pyrrole (**1**) and 2-[(2-aminomethyl)phenyl]pyrrole (**2**) involving Suzuki coupling and hydrogenation. The reaction conditions for the Suzuki coupling reaction of pyrrole with aryl halogenides bearing the substituent in the ortho-position were optimized. The reaction employs commercially available Pd catalyst and is applicable for different substituents, those with electron withdrawing as well as electron donating groups. Moreover, the unprotected amino-arylhalogenides could be used, and reaction could be employed for the construction of the quinazoline skeleton. The latter is under current investigation.

EXPERIMENTAL SECTION

General. ^{1}H- and ^{13}C-NMR spectra were recorded on a Brucker Spectrometer at 300 or 600 MHz. All NMR spectra were measured in $CDCl_3$ using tetramethylsilane as a reference. High-resolution mass spectra (HRMS) were measured on an Applied Biosystems 4800 Plus MALDI TOF/TOF instrument. Melting points were obtained using an Original Kofler apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer M-297 and ABB Bomem M-102 spectrophotometers. Silica gel (0.05–0.2 mm) was used for chromatographic purifications. Solvents were purified by distillation.

Suzuki reaction—general procedure. To a stirred solution of aryl halogenide (**4**, 0.95 mmol), cesium carbonate (1.89 mmol) and *tetrakis*(triphenylphosphine)palladium(0) (5 mol %) in toluene (20 mL) at reflux under nitrogen atmosphere, a solution of *N*-Boc-pyrrol-2-yl boronic acid (**3**, 0.95 mmol) in the mixture of toluene (10 mL) and methanol (3 mL) was added during 7 h. The mixture was stirred at reflux for 17 h, cooled and methanol was removed under reduced pressure. To a toluene suspension, water (30 mL) was added and the layers were separated. The water layer was extracted with CH_2Cl_2 (3× 25 mL). Combined organic extracts were washed with water (30 mL), dried over $MgSO_4$, and solvent was evaporated under reduced pressure. The resulting crude product was purified by chromatography on silica eluting with the mixture of (0 → 50%) diethyl ether in hexane to yield desired 2-phenylpyrrole.

N-Boc-2-(2-nitrophenyl)pyrrole (5a). This compound was obtained as yellow crystals, mp 78−79°C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.33 (s, 9H), 6.19 (dd, 1H, J = 3.3, 1.8 Hz), 6.27 (t, 1H, J = 3.3 Hz), 7.41 (dd, 1H, J = 3.3, 1.8 Hz), 7.43−7.54 (m, 2H), 7.62 (dt, 1H, J = 7.5, 1.3 Hz), 8.10 ppm (dd, 1H, J = 8.2, 1.1 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 27.4 (3C, q), 83.9 (1C, s), 110.7 (1C, d), 114.7 (1C, d), 122.5 (1C, d), 124.2 (1C, d), 128.5 (1C, d), 129.4 (1C, s), 129.9 (1C, s), 132.6 (1C, d), 132.7 (1C, d), 148.4 (1C, s), 148.7 ppm (1C, s). IR (KBr): 3453 (w), 2974 (w), 1747 (s), 1522 (s), 1351 (s), 1324 (s), 1147 (s), 976 (m), 722 cm^{-1} (m); HRMS: *m/z* [M + H]$^+$ calcd for $C_{15}H_{17}N_2O_4$: 289.1183; found: 289.1172.

N-Boc-2-[(2-tosylamino)phenyl]pyrrole (5c). This compound was obtained as pale pink powder; mp 174−177°C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.22 (s, 9H), 2.38 (s, 3H), 5.55 (dd, 1H, J = 3.2, 1.7 Hz), 6.17 (t, 1H, J = 3.3 Hz), 6.57 (br. s, 1H), 7.05 (d, 2H, J = 4.5 Hz), 7.20 (d, 2H, J = 8.1 Hz), 7.26−7.33 (m, 1H), 7.39 (dd, 1H, J = 3.2, 1.7 Hz), 7.56 (d, 2H, J = 8.1 Hz), 7.63 ppm (d, 1H, J = 8.1 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 21.4 (1C, q), 27.2 (3C, q), 84.1 (1C, s), 110.7 (1C, d), 115.4 (1C, d), 119.7 (1C, d), 122.8 (1C, d), 123.6 (1C, d), 125.9 (1C, s), 127.1 (2C, d), 127.6 (1C, s), 128.9 (1C, d), 129.4 (2C, d), 131.3 (1C, d), 135.6 (1C, s), 136.2 (1C, s), 143.7 (1C, s), 118.6 ppm (1C, s); IR (KBr): 3252 (s), 2984 (w), 2928 (w), 1732 (s), 1397 (s), 1335 (s), 1310 (s), 1171 (s), 1145 (s), 738 cm^{-1} (m); HRMS: *m/z* [M + K]$^+$ calcd for $C_{22}H_{24}KN_2O_4S$: 451.1088; found: 451.1066.

N-Boc-2-(2-cyanophenyl)pyrrole (5e). This compound was obtained as brown oil; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.39 (s, 9H), 6.26−6.33 (m, 2H), 7.39−7.45 (m, 3H), 7.54−7.61 (m, 1H), 7.65−7.69 ppm (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 27.5 (3C, q), 84.0 (1C, s), 110.8 (1C, d), 113.4 (1C, s), 116.2 (1C, d), 118.1 (1C, s), 123.2 (1C, d), 127.5 (1C, d), 129.9 (1C, s), 130.4 (1C, d), 131.9 (1C, d), 132.2 (1C, d), 138.3 (1C, s), 148.6 ppm (1C, s); IR (KBr): 3454 (m), 2983 (w), 2926 (w), 2367 (w), 2343 (w), 1748 (s), 1401 (m), 1340 (m), 1315 (s), 1150 (s), 975 (m), 842 (m), 765 cm^{-1} (m); HRMS: *m/z* [M + Na]$^+$ calcd for $C_{16}H_{16}N_2NaO_2$: 291.1104; found: 291.1110.

N-Boc-2-(3-cyanophenyl)pyrrole (5f). This compound was obtained as white solid; mp 74−76°C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.40 (br.s, 9H), 6.21−6.27 (m, 2H), 7.38 (dd, 1H, J = 3.1, 2.0 Hz), 7.42−7.49 (m, 1H), 7.55−7.62 (m, 2H), 7.63−7.67 ppm (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 27.6 (3C, q), 84.1 (1C, s), 110.7 (1C, d), 111.7 (1C, s), 115.6 (1C, d), 118.6 (1C, s), 123.4 (1C, d), 128.3 (1C, d), 130.4 (1C, d), 132.3 (1C, s), 132.6 (1C, d), 133.4 (1C, d), 135.4 (1C, s), 148.9 ppm (1C, s); IR (KBr): 3450 (w), 2231 (m), 1732 (s), 1473 (m), 1394 (m), 1374 (m), 1341 (m), 1323 (s), 1148 (m), 846 (m), 791 (m), 738 (m), 693 cm^{-1} (m); HRMS: *m/z* [M+Na]$^+$ calcd for $C_{16}H_{16}N_2NaO_2$: 291.1104; found: 299.1115.

Pyrrolo[1,2-c]quinazolin-5(6H)-one (8). This compound was obtained as white crystallinic solid; mp 263−265°C; ^{1}H-NMR (DMSO-d_6, 600 MHz) δ: 6.67 (t, 1H, J = 3.3 Hz), 7.00 (dd, 1H, J = 3.5, 1.4 Hz), 7.18−7.21 (m, 1H), 7.25 (dd, 1H, J = 8.1, 0.5 Hz), 7.30−7.34 (m, 1H), 7.59 (dd, 1H, J = 3.0, 1.4

Hz), 7.89−7.92 (m, 1H), 11.46 ppm (br.s, 1H); ^{13}C-NMR (DMSO-d_6, 150 MHz) δ: 104.4 (1C, d), 113.7 (1C, d), 114.3 (1C, s), 115.4 (1C, d), 115.5 (1C, d), 122.1 (1C, d), 122.9 (1C, d), 127.5 (1C, d), 129.1 (1C, s), 132.4 (1C, s), 145.4 ppm (1C, s); IR (KBr): 3448 (m), 1707 (s), 1596 (m), 1493 (m), 1408 (m), 1341 (w), 718 cm^{-1} (m); HRMS: *m/z* [M + H]$^+$ calcd for $C_{11}H_9N_2O$: 158.0709; found 185.0712.

General procedure for removal of Boc. A suspension of sodium methoxyde (freshly prepared by reacting 3.0 mmol of sodium with 10 mL of methanol) was added to a stirred solution of *N-tert*-butoxycarbonyl compound **5** (1.0 mmol) in methanol (20 mL) and stirred at reflux for 3 h, and at 25°C for additional 15 h. The solvent was evaporated, and the residue was partitioned between dichloromethane and water. Water layer was extracted with dichloromethane (2 × 25 mL), and the combined organic extracts were washed with brine (30 mL). Organic extracts were dried over $MgSO_4$, solvent was evaporated to give the products quantitatively, which were submitted to further purification by column chromatography on silica gel.

2-(2-Nitrophenyl)pyrrole (6a). This compound was obtained as orange oil; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 6.31 (dd, 1H, *J* = 5.8, 2.7 Hz), 6.46−6.51 (m, 1H), 6.91−6.94 (m, 1H), 7.31−7.38 (m, 1H), 7.55 (dt, 1H, *J* = 7.8, 1.2 Hz), 7.61 (dd, 1H, *J* = 7.8, 1.2 Hz), 7.69−7.75 (m, 1H), 8.91 ppm (br.s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 109.1 (1C, d), 110.9 (1C, d), 120.3 (1C, d), 124.3 (1C, d), 126.2 (1C, s), 126.8 (1C, s), 126.9 (1C, d), 130.6 (1C, d), 132.2 (1C, d), 148.0 ppm (1C, s); IR (KBr): 3343 (s), 1609 (w), 1523 (s), 1482 (m), 1360 (m), 1116 (m), 1036 (m), 851 (w), 827 (w), 745 (s), 679 (w), 591 cm^{-1} (w); HRMS: *m/z* [M+H]$^+$ calcd for $C_{10}H_9N_2O_2$: 189.0659; found: 189.0661.

2-(2-Cyanophenyl)pyrrole (6e). This compound was obtained as white solid; mp 84−86°C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 6.30−6.38 (m, 1H), 6.77−6.85 (m, 1H), 6.99−7.00 (m, 1H), 7.20−7.27 (m, 1H), 7.51−7.58 (m, 1H), 7.60−7.67 (m, 2H), 9.18 ppm (br. s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 105.9 (1C, s), 110.2 (1C, d), 110.3 (1C, d), 120.0 (1C, s), 120.8 (1C, d), 125.8 (1C, d), 126.5 (1C, d), 128.1 (1C, s), 133.0 (1C, d), 133.9 (1C, d), 135.6 ppm (1C, s). IR (KBr): 3331 (m), 2228 (m), 1599 (w), 1486 (w), 1463 (w), 1135 (m), 1042 (m), 758 (s), 724 (s), 603 cm^{-1} (w); HRMS: *m/z* [M+H]$^+$ calcd for $C_{11}H_9N_2$: 169.0760; found: 169.0753.

2-(3-Cyanophenyl)pyrrole (6f). This compound was obtained as white solid; mp 95−97°C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 6.33 (dd, 1H, *J* = 6.0, 2.6 Hz), 6.56−6.63 (m, 1H), 6.88−6.96 (m, 1H), 7.40−7.50 (m, 2H), 7.66−7.70 (m, 1H), 7.74 (br. s, 1H), 8.55 ppm (br.s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 107.5 (1C, d), 110.6 (1C, d), 112.9 (1C, s), 118.7 (1C, s), 120.2 (1C, d), 126.9 (1C, d), 127.7 (1C, d), 129.1 (1C, d), 129.6 (1C, d), 133.8 ppm (1C, s), 1C is not seen; IR (KBr): 3372 (s), 3365 (s), 2234 (s), 1605 (m), 1468 (m), 1136 (w), 1042 (m), 884 (m), 795(s), 723 (s), 682 (s), 587 cm^{-1} (m); HRMS: *m/z* [M+H]$^+$ calcd for $C_{11}H_9N_2$: 169,0760; found: 169.0736.

General procedure for hydrogenation. Compounds **6a** or **6e** (98 mg or 20 mg, respectively) were submitted to hydrogenation on 10% Pd-C (30 mg or 10 mg, respectively) in absolute methanol (50 mL or 20 mL, respectively) in a Paar apparatus at 60 psi at room temperature for 8 or 2 h, respectively. The catalyst was filtered off, and the solvent was evaporated under reduced pressure to afford crude products of amino derivatives **1** and **2** in 63% and 58% yield, respectively. After column chromatography on silica gel, **1** and **2** were isolated in 30% and 28% yield, respectively. It should be noted that this is not surprising as many of the unprotected pyrrole derivatives are generally known to be unstable, especially those substituted with electron donating groups.

2-(2-Aminophenyl)pyrrole (1). This compound was obtained as white solid; mp 103−106°C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.94 (br.s, 2H), 6.31 (dd, 1H, *J* = 6.0, 2.7 Hz), 6.40−6.44 (m, 1H), 6.76 (dd, 1H, *J* = 7.8, 0.9 Hz), 6.81 (dt, 1H, *J* = 7.5, 1.2 Hz), 6.86 (dd, 1H, *J* = 2.7, 1.5 Hz), 7.08 (dt, 1H, *J* = 7.8, 1.6 Hz), 7.24 (dd, 1H, *J* = 7.6, 1.4 Hz), 8.59 ppm (br.s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 107.2 (1C, d), 109.3 (1C, d), 116.4 (1C, d), 117.9 (1C, d), 119.0 (1C, d), 119.6 (1C, s), 127.7 (1C, d), 128.3 (1C, d), 129.5 (1C, s), 143.3 ppm (1C, s); IR (KBr): 3373 (s), 3300 (m), 3204 (m), 1614 (m), 1563 (m), 1497 (m), 1468 (m), 1302 (m), 1137 (m), 1116 (m), 755 (s), 714 cm^{-1} (s); HRMS: *m/z* [M]+ calcd for $C_{10}H_{10}N_2$: 158.0838; found: 158.0831 [41].

2-[(2-Aminomethyl)phenyl]pyrrole (2). This compound was obtained as yellow oil; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.72 (br.s, 2H), 3.91 (s, 2H), 6.27−6.32 (m, 1H), 6.43−6.47 (m, 1H), 6.87−6.91 (m, 1H), 7.16 (dt, 1H, *J* = 7.4, 1.3 Hz), 7.22−7.24 (m, 1H), 7.31 (dt, 1H, *J* = 7.6, 1.5 Hz), 7.61 (dd, 1H, *J* = 7.7, 1.2 Hz), 12.60 ppm (br. s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 46.2 (1C, t), 106.8 (1C, d), 108.7 (1C, d), 118.4 (1C, d), 125.9 (1C, d), 128.1 (1C, d), 128.8 (1C, d), 130.9 (1C, d), 132.7 (1C, s), 134.6 (1C, s), 135.3 ppm (1C, s); IR (KBr): 3434 (s), 2922 (w), 2598 (w), 1486 (m), 1103 (m), 761 (s), 717 cm^{-1} (s); HRMS: *m/z* [M+H]$^+$ calcd for $C_{11}H_{13}N_2$: 173.1073; found: 173.1069.

2-(2-Tolyl)pyrrole (9). This compound was obtained as colorless oil; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.45 (s, 3H), 6.30−6.33 (m, 1H), 6.33−6.36 (m, 1H), 6.85−6.87 (m, 1H), 7.16−7.26 (m, 3H), 7.33−7.35 (m, 1H), 8.24 ppm (br. s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 21.1 (1C, q), 108.7 (1C, d), 109.1 (1C, d), 117.8 (1C, d), 125.9 (1C, d), 126.7 (1C, d), 127.8 (1C, d), 130.9 (1C, d), 131.2 (1C, s), 132.8 (1C, s), 135.0 ppm (1C, s); IR (KBr): 3423 (s), 2922 (w), 1489 (m), 1466 (m), 1099 (m), 1035 (m), 757 (s), 718 cm^{-1} (s); HRMS: *m/z* [M+H]$^+$ calcd for $C_{11}H_{12}N$: 158.0964; found: 158.0967 [42].

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