JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.0c01700 • Publication Date (Web): 21 Sep 2020

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Electrosynthesis of 2-(1,3,4-Oxadiazol-2-yl)aniline Derivatives with Isatins as Amino-attached C1 Sources

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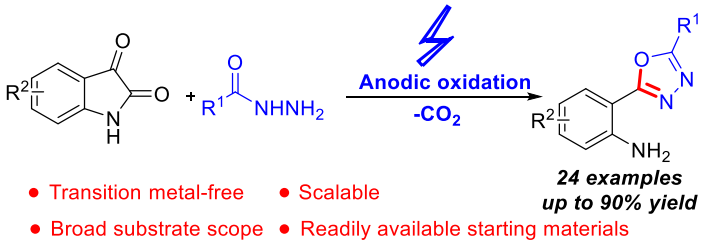


ABSTRACT: An intramolecular decarboxylative coupling reaction for the construction of 2-(1,3,4-oxadiazol-2-yl)aniline derivatives was developed from readily available isatins and hydrazides by virtue of electrochemistry. In this reaction, isatins were employed as amino-attached C1 sources, providing a variety of 2-(1,3,4-oxadiazol-2-yl)aniline derivatives with moderate to good yields.

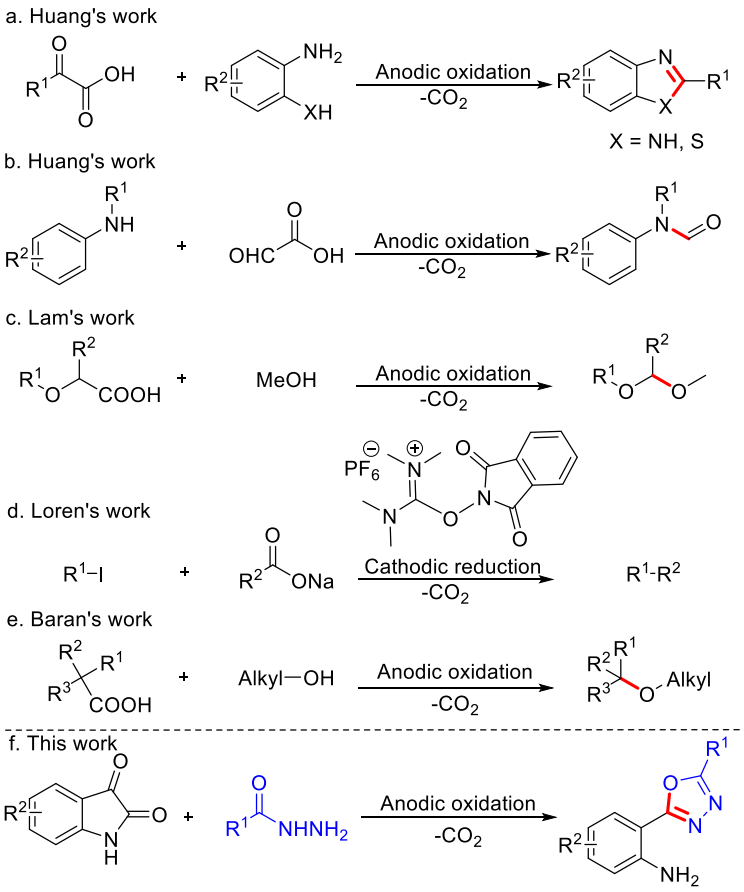
INTRODUCTION

Decarboxylative coupling has attracted tremendous attention since it emerged as a fascinating approach for the construction of C–C bond and C–heteroatom bond.[1] However, transition metal catalysts were generally required for achieving efficient transformation.[2] The residues of metal catalysts restricted their wide applications, especially for the synthesis of heterocyclic ring compounds. Furthermore, previous works mainly focused on the formation of C–C bond and C–N bond, few reports were available for the construction of C–

O bond in the heterocyclic ring compounds. Therefore, it is still highly desirable to construct C–O bond in the heterocyclic ring compounds under metal free conditions via a decarboxylative coupling process.

Organic electrochemistry represents a facile and green approach for various transformation since it uses traceless electron as reagents.[3] Recently, organic electrosynthesis gained considerable progress, especially in the past decades. Some elegant decarboxylative coupling reactions were developed by the group of Huang,[4] Lam,[5] Loren,[6] Baran,[7] Lei[8] and Zeng.[9] For instance, in 2016, Huang reported an electrochemical method for the synthesis of 2-substituted benzimidazole via decarboxylative coupling of *a*-keto acids with *ortho*-phenylenediamines (Scheme 1a).[4a] In 2018, the group of Huang achieved the decarboxylative *N*-formylation of amines with glyoxylic acid via electrochemistry (Scheme 1b). [4c] Lam developed an electrochemical oxidation of α-alkoxyl carboxylic acids to give substituted acetals in 2018 (Scheme 1c).[5] Recently, an electrochemical nickel-catalyzed decarboxylative sp^2-sp^3 cross-coupling reaction of *in situ* generated *N*-hydroxyphthalimide esters and aryl iodides was disclosed by Loren (Scheme 1d).[6] Moreover, Baran reported a practical method for the formation of C–O bond and applied to the synthesis of sterially hindered ether via electrocatalytic decarboxylative coupling (Scheme 1e).[7] Inspired by these works and our interests on the electrosynthesis of heterocyclic ring compounds,[10] we herein reported a facile intramolecular decarboxylative coupling reaction for the electrosynthesis of 2-(1,3,4-oxadiazol-2-yl)aniline derivatives with isatins as amino-attached C1 sources (Scheme 1c). The 2-(1,3,4-oxadiazol-2-yl)aniline are important class of oxygen-containing heterocycles.[11] Furthermore, the free NH_2 generated from this electrocatalytic reaction provides the possbility for further manipulation. The preparation of 2-(1,3,4-oxadiazol-2-yl)aniline were reported by Wu[12] and Guo,[13] employing CuI as catalyst for 48 h and Eosin Y as photocatalyst for 24 h, respectively. With our developed approach, the 2-(1,3,4-oxadiazol-2-yl)aniline were constructed smoothly in moderate to good yields within 2 h without the requirement of metal or photocatalyst.

Scheme 1. Electrochemical Decarboxylative Cross-Coupling Reactions



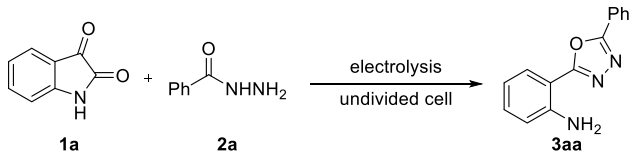
RESULTS AND DISCUSSION

Our initial investigation began by electrolyzing isatin (**1a**) and benzoylhydrazine (**2a**) in the presence of K_2CO_3 at a constant current of 10 mA with KI as electrolyte. To our delight, the desired product can be obtained in a yield of 79% (entry 1, Table 1). Firstly, the reaction temperature was investigated and 120 °C turned out to be the optimal reaction temperature (entries 1–5). Then, we screened the reaction solvent. Experimental results indicated that the DMSO gave superior results than DMA, DMF and NMP (entries 6–8). Subsequently, various halide salts were explored, and KI show better performence than other halide salts, including *n*-Bu_4NI, Me_4NI and KBr (entries 9–11). Moreover, when the reaction was performed in the absence of KI, the reaction yield decreased sharply (entry 12). On the other hand, the reaction proceeded smoothly to afford the desired product with 75% and 61% yield when the amount of KI decreased to 50 mol% and 20 mol%, respectively (entries 13 and 14). These results suggested KI also serves as the mediator for the reaction. Furthermore, various bases were also examined (entries 15-17), and K_2CO_3 was still the optimal base for this transformation. Changing the values of current also decreased the

reaction yields (entries 18 and 19). Finally, no desired product was detected when the reaction was carried out without the pass of electricity (entry 20). This result suggested the pass of electricity was necessary for the reaction.

By using the optimal electrolytic reaction conditions, the generality of this developed electrocatalytic decarboxylative coupling reaction was explored. As shown in Table 2, various hydrazides were conducted smoothly to give the corresponding 2-(1,3,4-oxadiazol-2-yl)aniline in moderate to good yields (entries 1-16). The benzoylhydrazines with electron-donating substituents on the aromatic ring gave superior results than electron-withdrawing substituents (entries 2-4 vs 9). Moreover, the halide substituted benzoylhydrazines were compatible with the standard conditions to

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3aa

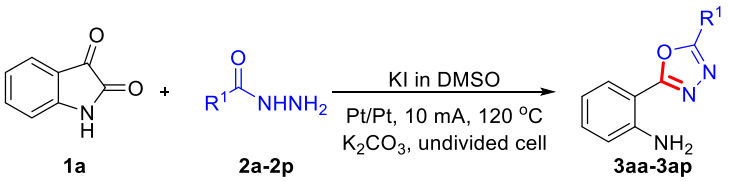
entry	electrolyte	solvent	base	I (mA)	T (°C)	yield[b] (%)
1	KI	DMSO	K_2CO_3	10	120	79
2	KI	DMSO	K_2CO_3	10	110	70
3	KI	DMSO	K_2CO_3	10	130	67
4	KI	DMSO	K_2CO_3	10	50	28
5	KI	DMSO	K_2CO_3	10	rt	15
6	KI	DMA	K_2CO_3	10	120	59
7	KI	DMF	K_2CO_3	10	120	trace
8	KI	NMP	K_2CO_3	10	120	15
9	*n*-Bu_4NI	DMSO	K_2CO_3	10	120	48
10	Me_4NI	DMSO	K_2CO_3	10	120	42

11	KBr	DMSO	K_2CO_3	10	120	30
12	$LiClO_4$	DMSO	K_2CO_3	10	120	20
13[c]	KI	DMSO	K_2CO_3	10	120	75
14[d]	KI	DMSO	K_2CO_3	10	120	61
15	KI	DMSO	Na_2CO_3	10	120	69
16	KI	DMSO	KOH	10	120	66
17	KI	DMSO	K_3PO_4	10	120	45
18	KI	DMSO	K_2CO_3	15	120	74
19	KI	DMSO	K_2CO_3	5	120	59
20	KI	DMSO	K_2CO_3	0	120	n.d.

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), electrolyte (0.3 mmol), Base (0.3 mmol), Solvent (3 mL) , Pt/Pt (1.0 x 1.0 cm^2); the electrolysis was conducted in an undivided cell at oil bath (120 °C) for 2 h (2.5 F). [b]Yields of the isolated products. [c]The loading of KI was 50 mol %. [d]The loading of KI was 20 mol %

afford the desired products with 47-90% yields (entries 5-8). Notably, furan-2-carbohydrazide (**2j**) and thiophene-2-carbohydrazide (**2k**) proceeded smoothly, providing the corresponding products with 62% and 69% yields, respectively (entries 10 and 11). Gratifyingly, the more challenging substrates containing amino groups were proved to be compatible with the standard conditions, giving the desired products in moderate yields (entries 12 and 13). However, when the benzoylhydrazine bearing a hydroxyl group was employed, only a trace amount of the desired product was detected (entry 14). Furthermore, when alkylhydrazides were employed as substrates, such as acetohydrazide, butyrohydrazide, the reactions proceeded smoothly to give the desired products in 57% and 51% yields, respectively (entries 15 and 16).

Table 2. The Scope of Hydrazides[a]



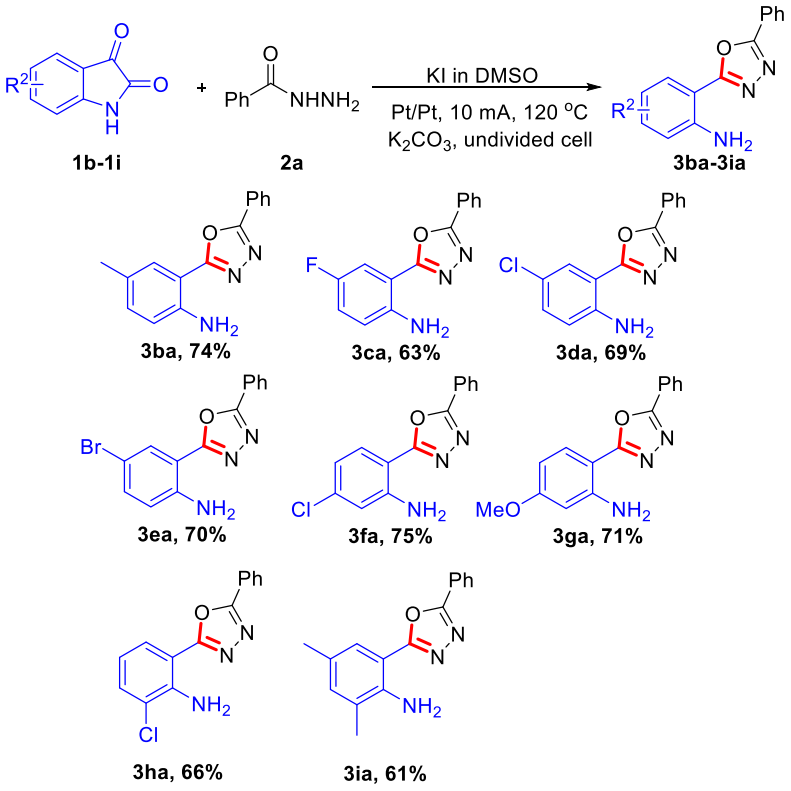
1a 2a-2p 3aa-3ap

entry	R^1	product	yield[b] (%)
1	Ph (**2a**)	**3aa**	77
2	4-Me-Ph (**2b**)	**3ab**	83
3	3-Me-Ph (**2c**)	**3ac**	76
4	4-OMe-Ph (**2d**)	**3ad**	84
5	4-Cl-Ph (**2e**)	**3ae**	90
6	2-Cl-Ph (**2f**)	**3af**	73
7	4-F-Ph (**2g**)	**3ag**	76
8	2-F-Ph (**2h**)	**3ah**	47
9	4-CF_3-Ph (**2i**)	**3ai**	72
10	2-furnal (**2j**)	**3aj**	62
11	2-thienyl (**2k**)	**3ak**	69
12	2-NH_2-Ph (**2l**)	**3a1**	46
13	4-NH_2-Ph (**2m**)	**3am**	70
14	4-OH-Ph (**2n**)	**3an**	trace
15	Me (**2o**)	**3ao**	57
16	*n*-Pr (**2p**)	**3ap**	51

[a]Reaction conditions: **1a** (0.3 mmol), **2a-2p** (0.3 mmol), KI (0.3 mmol), K_2CO_3 (0.3 mmol), DMSO (3 mL), Pt/Pt (1.0 x 1.0 cm^2); the electrolysis was conducted in an undivided cell at oil bath (120 °C) for 2 h (2.5 F). [b]The isolated yields.

Subsequently, various isatins were also investigated under standard conditions (Scheme 2). Both electron-donating and electron-withdrawing substituents on the aromatic cyclic performed smoothly to give the corresponding products in moderate yields (**3ba-3ia**). Moreover, the halide substituted group, including fluoro, chloro, bromo, were also conducted smoothly to produce the desired products with 63-75% yields (**3ca-3fa** and **3ha**). Furthermore, a little steric effect was found since the 5-chloro isatin gave a better result than 6-chloro isatin (**3fa** vs **3ha**).

Scheme 2. **The Scope of Isatins**

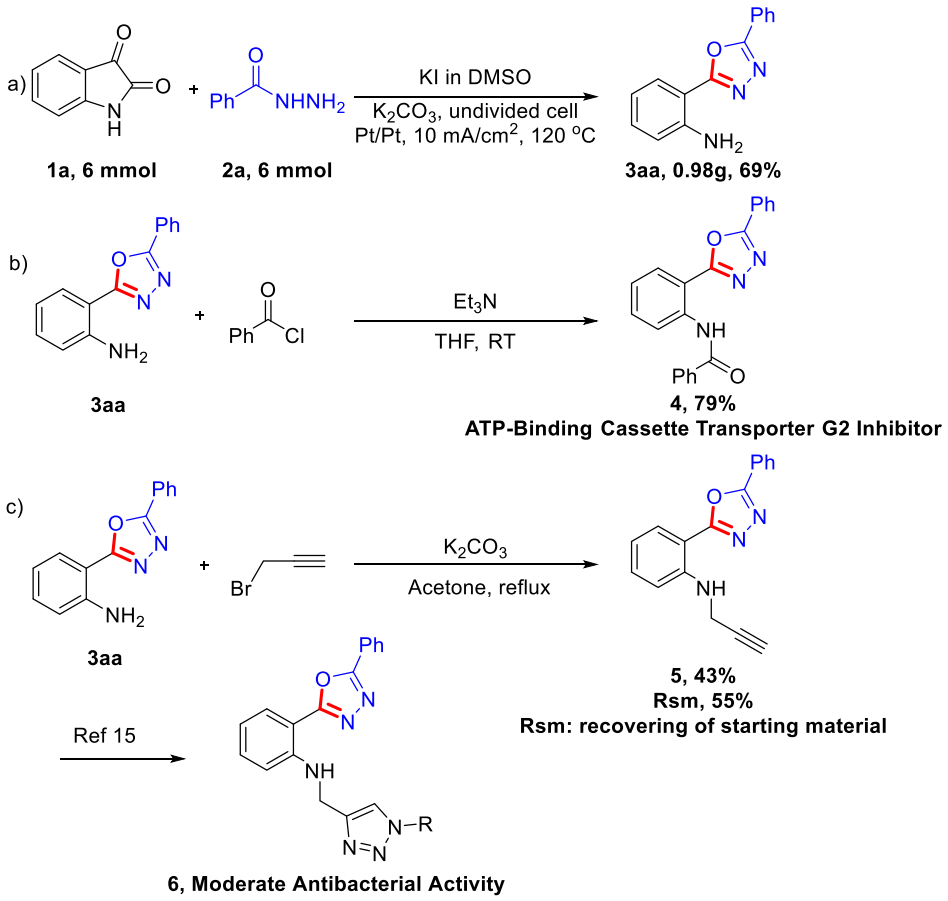


[a] Reaction conditions: **1b-1i** (0.3 mmol), **2a** (0.3 mmol), KI (0.3 mmol), K_2CO_3 (0.3 mmol), DMSO (3 mL) , Pt/Pt (1.0 x 1.0 cm^2); the electrolysis was conducted in an undivided cell at oil bath (120 °C) for 2 h (2.5 F). [b] The isolated yields.

Then, we performed a gram scale experiment, employing 6 mmol of isatin (**1a**) and 6 mmol of benzoylhydrazine (**2a**) with 50 mol% of KI. Gratifyingly, the reaction proceeded smoothly to produce the desired product **3aa** with a satisfactory yield of 69% (Scheme 3a), demonstrating the practicality of this approach. Moreover, the desired product **3aa** could be

further converted to *N*-(2-(5-phenyl-1,3,4-oxadiazol-2-yl)phenyl)benzamide **4**, which served as ATP-binding cassette transporter G2 inhibitor (Scheme 3b).[14] Furthermore, the desired product **3aa** could react with 3-bromoprop-1-yne to generate 2-(5-phenyl-1,3,4-oxadiazol-2-yl)-*N*-(prop-2-yn-1-yl)aniline **5**, which was an important intermediate for the construction of 2-(5-Phenyl-1,3,4-oxadiazol-2-yl)-*N*-[(1-aryl-1H-1,2,3-triazol-4-yl)methyl]anilines **6** (Scheme 3c). The 2-(5-Phenyl-1,3,4-oxadiazol-2-yl)-*N*-[(1-aryl-1H-1,2,3-triazol-4-yl)methyl]anilines **6** showed moderate antibacterial activity.[15]

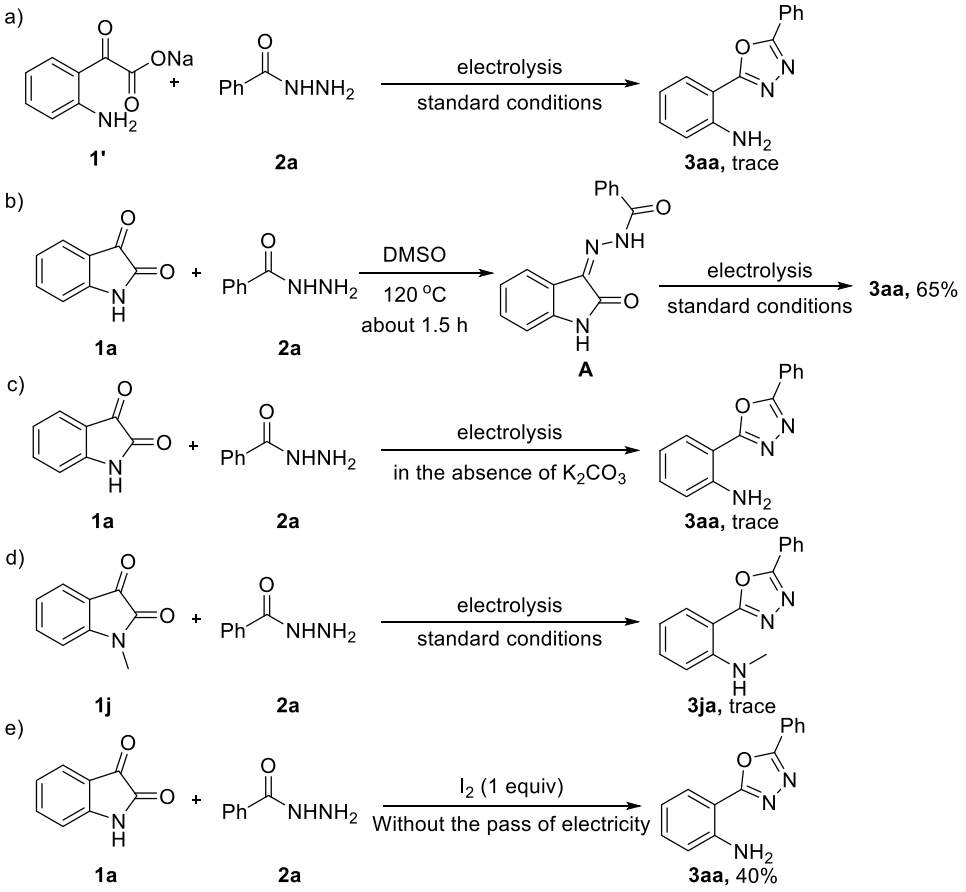
Scheme 3. The Scale-up Reaction and Its Synthetic Applications



To gain more insight into the reaction mechanism, some control experiments were performed (Scheme 4). Initially, the compound of sodium 2-(2-aminophenyl)-2-oxoacetate (**1'**) was synthesized and electrolyzed under standard conditions, only a trace amount of desired product was detected (Scheme 4a). The result suggestted that the salt 2-(2-aminophenyl)-2-oxoacetate was not involved in the reaction. Then isatin and

benzoylhydrazine were heated at 120 °C in DMSO until the disappearance of reactants (about 1.5 h), giving the corresponding condensation product A in almost quantitative yield. Subequently, KI and K_2CO_3 were added and the resulting mixture was electrolyzed under standard conditions, the desired product **3aa** could be obtained in 65% yield (Scheme 4b). This result indicated that the condensation product A was likey to be an intermediate for this reaction. Moreover, no desired product **3aa** was detected when the reaction was electrolyzed in the absence of K_2CO_3 (Scheme 4c). Furthermore, only a trace amount of corresponding product **3ja** was detected when *N*-methyl isatin was employed under standard conditions (Scheme 4d). These results indicated that both K_2CO_3 and free N-H were necessary for the ring opening of corresponding condensation product A generated *in situ*. Finally, the desired product **3aa** can be obtained in 40% yield when molecular iodine was employed as an oxidant in place of electricity (Scheme 4e). This result showed that molecular iodine should be the active species for the reaction.

Scheme 4. Control Experiments



Moreover, Cyclic voltammetric (CV) experiments were also conducted to investigate this reaction. CV results indicated that iodide ion show two oxidation waves at 0.44 V and 0.71 V vs Ag/AgCl, repectively (Figure. 1). The desired product **3aa** exhibited an oxidation wave ~0. 62 V vs Ag/AgCl (Figure. 2). These results indicated that the iodide ion is proned to be oxidized than the desired product **3aa**, making it possibe for the tolerence of NH_2 group under electrolysis conditions.

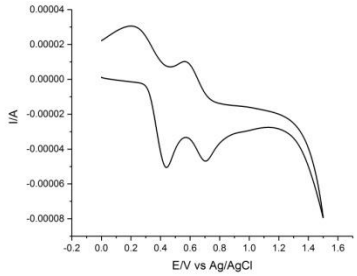


Figure. 1 Cyclic voltammogram of KI (5 mM) in 0.1 M $LiClO_4$/DMSO, using a Pt disk as the working electrode, and Pt wire and Ag/AgCl as the counter and reference electrodes, respectively, at a scan rate of 100 mV/s.

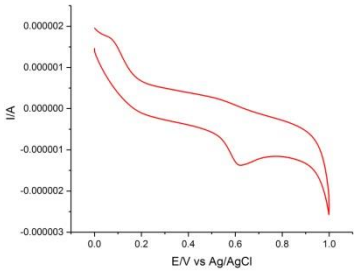
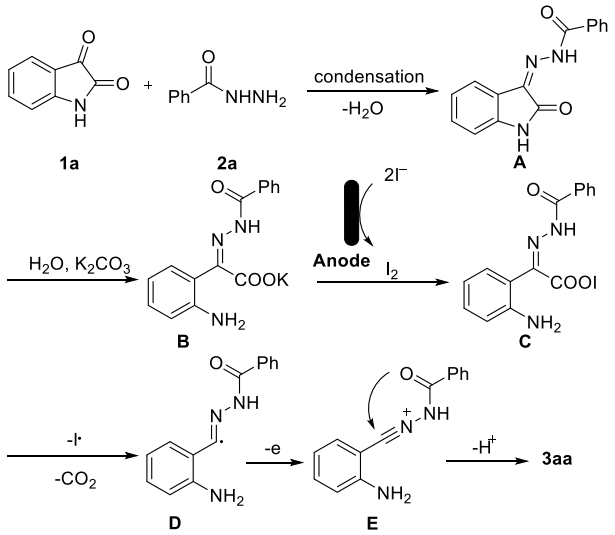


Figure. 2 Cyclic voltammogram of **3aa** (5 mM) in 0.1 M $LiClO_4$/DMSO, using a Pt disk as the working electrode, and Pt wire and Ag/AgCl as the counter and reference electrodes, respectively, at a scan rate of 100 mV/s.

According to the aboved results and previous reports,[9,12,13] a possible reaction mechanism was proposed based on the reaction of isatin (**1a**) and benzoylhydrazine (**2a**). As shown in Scheme 5, the condenstion reaction occurs between **1a** and **2a** to form acylhydrazone **A**.[12] The formed acylhydrazone can be easily hydrolyzed in the presence of K_2CO_3 to give potassium carboxylate **B**. Meanwhile, the iodide ion is oxidized to be molecular iodine at anode, which could react with **B** to generate intermediate **C**. The

intermediate **C** is unstable and easily losses an iodine radical, followed by the liberation of carbon dioxide to give the corresponding carbon center radical **D**.[9,13] The carbon center radical **D** can be further oxidized, followed by reaction with intramolecular masked O reagent to give the desired product **3aa**.

Scheme 5. The Proposed Reaction Mechanism



In summary, we have developed a facile approach for the construction of C-O bond and demonstrated its application for the synthesis of 2-(1,3,4-oxadiazol-2-yl)aniline derivatives under metal free conditions. This electrocatalytic protocol features a wide scope of substrate, readily available starting materials, short reaction time and scalability. Moreover, the generated NH_2 group can be well-tolerated and further manipulated. More reactions for the synthesis of other heterocycles by virtue of this electrocatalytic protocol are ongoing in our laboratory.

EXPERIMENTAL SECTION

General Information: All products were characterized by ^{1}H NMR and ^{13}C{^{1}H}NMR, using TMS as an internal reference (^{1}H NMR: 400MHz, ^{13}C{^{1}H}NMR: 100MHz). HRMS (ESI) data were recorded on a Q-TOF Premier. Commercial reagent and compound were used without purification.

Preparation of Substrates: Substrates **1a-1j** and **2a-2p** are commercially available. Substrate 1' was synthesized according to the previous literature procedure.[16]

Representative Procedures for the Synthesis of 2-(1,3,4-Oxadiazol-2-yl)aniline Derivatives: An undivided cell was equipped with a magnet stirrer, two platinum plates (1.0 x 1.0 cm^2, commercially available from GaossUnion, China) electrodes as the working electrode and counter electrode. In the electrolytic cell, a mixture of isatins **1** (0.3 mmol), hydrazides **2** (0.3 mmol), KI (0.3 mmol, 49.8 mg) and DMSO (3 mL) was allowed to stir and electrolyze at a constant current conditions (10 mA) under 120 °C (2 h, 2.5 F). Then the solvent was removed with a rotary evaporator and the residue was purified by column chromatography on silica gel to afford the desired product. The product was dried under high vacuum for at least 0.5 h before it was weighed and characterized by NMR spectroscopy.

Gram-Scale Synthesis of 3aa

An undivided cell was equipped with a magnet stirrer, two platinum plates (1.5 x 1.5 cm^2) electrodes as the working electrode and counter electrode. In the electrolytic cell, a mixture of isatin **1a** (6 mmol), benzoylhydrazine **2a** (6 mmol), KI (3 mmol, 498 mg) and DMSO (60 mL) was allowed to stir and electrolyze at a constant current conditions (23 mA) under 120 °C until the reaction intermediate finished (about 22 h, 3.1 F). Then the solvent was removed with a rotary evaporator and the residue was recrystallized by EtOAc to afford the desired product (0.98 g, 69% yield).

Synthesis of Compound 4

The compound **4** was prepared according to the literature procedure[14] and purified by column chromatography (petroleum ether / ethyl acetate = 15:1) to give the product as a colorless solid: 79% yield, (135 mg); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 11.9 (br, 1H), 9.08 – 9.05 (m, 1H), 8.23 – 8.07 (m, 5H), 7.64 − 7.57 (m, 7H), 7.29 – 7.25 (m, 1H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz, ppm): δ = 166.2, 164.1, 163.6, 138.8, 134.6, 133.1, 132.2, 132.0, 129.2, 128.9, 127.7, 127.6, 127.1, 123.3, 123.2, 120.9, 110.6.[14]

Synthesis of Compound 5

The compound **5** was prepared according to the literature procedure[15] and purified by column chromatography (petroleum ether / ethyl acetate = 15:1) to give the product as a colorless solid: 43% yield, (56 mg) ; ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ = 8.16 – 8.12 (m, 2H), 7.98 (dd, J = 8.0

Hz, J = 1.6 Hz, 1H), 7.68 − 7.60 (m, 4H), 7.49 – 7.45 (m, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.85 (t, J = 8.0 Hz, 1H), 4.24 (dd, J = 6.0 Hz, J = 2.4 Hz, 2H), 3.21 (t, J = 2.4 Hz, 1H); $^{13}C\{^{1}H\}$NMR (DMSO-d_6, 100 MHz, ppm): δ = 164.5, 162.7, 146.6, 133.4, 132.5, 129.9, 128.8, 127.2, 123.7, 116.8, 112.3, 105.9, 81.7, 74.2, 32.4.[15]

2-(5-Phenyl-1,3,4-oxadiazol-2-yl)aniline **(3aa)**[12]

The title compound was prepared according to the general working procedure and purified by column chromatography (petroleum ether / ethyl acetate = 10:1) to give the product as a light yellow solid: 77% yield, (55 mg); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.16 – 8.12 (m, 2H), 7.86 − 7.84 (m, 1H), 7.55 − 7.51 (m, 3H), 7.30 − 7.26 (m, 1H), 6.82 – 6.77 (m, 2H), 5.90 (br, 2H); $^{13}C\{^{1}H\}$NMR ($CDCl_3$, 100 MHz, ppm): δ = 164.6, 162.7, 147.1, 132.5, 131.6, 129.0, 127.8, 126.9, 123.8, 116.8, 116.2, 105.7.

2-(5-(p-Tolyl)-1,3,4-oxadiazol-2-yl)aniline **(3ab)** [12]

The title compound was prepared according to the general working procedure and purified by column chromatography (petroleum ether / ethyl acetate = 10:1) to give the product as a light yellow solid: 83% yield, (63 mg); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.02 – 8.00 (m, 2H), 7.85 − 7.83 (m, 1H), 7.33 − 7.31 (m, 2H), 7.29 − 7.25 (m, 1H), 6.82 – 6.76 (m, 2H), 5.41 (br, 2H), 2.43 (s, 3H); $^{13}C\{^{1}H\}$NMR ($CDCl_3$, 100 MHz, ppm): δ = 164.3, 162.8, 146.9, 142.1, 132.3, 129.7, 127.7, 126.8, 121.0, 116.8, 116.2, 105.8, 21.6.

2-(5-(m-Tolyl)-1,3,4-oxadiazol-2-yl)aniline **(3ac)** [13]

The title compound was prepared according to the general working procedure and purified by column chromatography (petroleum ether / ethyl acetate = 10:1) to give the product as a light yellow solid: 76% yield, (57 mg); ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ = 7.93 − 7.83 (m, 3H), 7.49 − 7.40 (m, 2H), 7.28 (t, J = 7.6 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 6.79 (br, 2H), 6.70 (t, J = 7.4 Hz, 1H), 2.40 (s, 3H); $^{13}C\{^{1}H\}$NMR ($CDCl_3$, 100 MHz, ppm): δ = 164.5, 162.9, 147.0, 138.9, 132.4, 128.9, 127.8, 127.4, 124.1, 123.7, 116.8, 116.2, 105.8, 21.3.

2-(5-(4-Methoxyphenyl)-1,3,4-oxadiazol-2-yl)aniline **(3ad)** [12]

The title compound was prepared according to the general working procedure and purified by column chromatography (petroleum ether / ethyl acetate = 8:1) to give the product as a light yellow solid: 84% yield, (67 mg); ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ = 8.03 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 7.9 Hz, 1H), 7.26 (t, J = 7.4 Hz, 1H), 7.12 (d, J = 8.5 Hz, 2H), 6.92 (d, J = 8.3 Hz, 1H), 6.78 (br, 2H), 6.69 (t, J = 7.4 Hz, 1H), 3.83 (s, 3H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz, ppm): δ = 164.1, 162.7, 162.3, 147.0, 132.3, 128.7, 127.7, 116.8, 116.4, 116.1, 114.5, 105.9, 55.5.

2-(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)aniline **(3ae)** [12]

The title compound was prepared according to the general working procedure and purified by column chromatography (petroleum ether / ethyl acetate = 8:1) to give the product as a light yellow solid: 90% yield, (73 mg); ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ = 8.14 (d, J = 7.9 Hz, 2H), 7.85 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.29 (t, J = 7.7 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.78 (br, 2H), 6.70 (t, J = 7.5 Hz, 1H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz, ppm): δ = 164.7, 161.9, 147.1, 137.9, 132.6, 129.4, 128.1, 127.8, 122.3, 116.9, 116.3, 105.5.

2-(5-(2-Chlorophenyl)-1,3,4-oxadiazol-2-yl)aniline **(3af)** [12]

The title compound was prepared according to the general working procedure and purified by column chromatography (petroleum ether / ethyl acetate = 10:1) to give the product as a light yellow solid: 73% yield, (59 mg); ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ = 8.13 (d, J = 7.6 Hz, 1H), 7.76 (d, J = 7.9 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.64 (t, J = 7.3 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 6.81 (br, 2H), 6.69 (t, J = 7.6 Hz, 1H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz, ppm): δ = 165.1, 161.2, 147.1, 133.1, 132.7, 132.3, 131.3, 131.1, 128.1, 127.1, 123.1, 116.9, 116.2, 105.6.

2-(5-(4-Fluorophenyl)-1,3,4-oxadiazol-2-yl)aniline **(3ag)**

The title compound was prepared according to the general working procedure and purified by column chromatography (petroleum ether / ethyl acetate = 10:1) to give the product as a light yellow solid: 76% yield, (58 mg); ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ = 8.19 – 8.16 (m, 2H), 7.85 (d, J = 8.0 Hz, 1H), 7.45 (t, J = 8.6 Hz, 2H), 7.28 (t, J = 7.7 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 6.78 (br,

2H) , 6.70 (t, J = 7.6 Hz, 1H); $^{13}C\{^{1}H\}$NMR ($CDCl_3$, 100 MHz, ppm): δ = 164.7 (d, J = 251.6 Hz), 164.6, 161.9, 147.1, 132.5, 129.1 (d, J = 8.8 Hz), 127.7, 120.2 (d, J = 3.1 Hz), 116.8, 116.5, 116.2 (d, J = 4.4 Hz), 105.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{11}N_3OF$ 256.0886; Found: 256.0888.

2-(5-(2-Fluorophenyl)-1,3,4-oxadiazol-2-yl)aniline **(3ah)**

The title compound was prepared according to the general working procedure and purified by column chromatography (petroleum ether / ethyl acetate = 10:1) to give the product as a light yellow solid: 47% yield, (36 mg); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.16 – 8.12 (m, 1H), 7.87 − 7.85 (m, 1H), 7.57 − 7.51 (m, 1H), 7.34 − 7.25 (m, 3H), 6.83 – 6.77 (m, 2H), 5.88 (br, 2H); $^{13}C\{^{1}H\}$NMR ($CDCl_3$, 100 MHz, ppm): δ = 164.9, 160.1 (d, J = 256.9 Hz), 159.6 (d, J = 5.1 Hz), 147.1, 133.3 (d, J = 8.4 Hz), 132.6, 129.6 (d, J = 1.2 Hz), 128.0, 124.6 (d, J = 3.7 Hz), 117.0 (d, J = 20.7 Hz), 116.8, 116.2, 112.4 (d, J = 11.6 Hz), 105.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{11}N_3OF$ 256.0886; Found: 256.0888.

2-(5-(4-(Trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)aniline **(3ai)**

The title compound was prepared according to the general working procedure and purified by column chromatography (petroleum ether / ethyl acetate = 10:1) to give the product as a light yellow solid: 72% yield, (66 mg); ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ = 8.34 (d, J = 8.04 Hz, 2H), 7.98 (d, J = 8.24 Hz, 2H), 7.89 − 7.87 (m, 1H), 7.32 − 7.28 (m, 1H), 6.94 – 6.92 (m, 1H), 6.79 (br, 2H), 6.44 – 6.70 (m, 1H); $^{13}C\{^{1}H\}$NMR ($CDCl_3$, 100 MHz, ppm): δ = 165.2, 161.6, 147.3, 133.2 (q, J = 32.7 Hz), 132.9, 127.8, 127.2, 127.1, 126.1 (q, J = 3.7 Hz), 123.6 (q, J = 270.8 Hz), 116.9, 116.3, 105.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{11}N_3OF_3$ 306.0854; Found: 306.0858.

2-(5-(Furan-2-yl)-1,3,4-oxadiazol-2-yl)aniline **(3aj)** [12]

The title compound was prepared according to the general working procedure and purified by column chromatography (petroleum ether / ethyl acetate = 8:1) to give the product as a light yellow solid: 62% yield, (42 mg); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.84 − 7.81 (m, 1H), 7.68 − 7.67 (m, 1H), 7.30 − 7.26 (m, 1H), 7.23 − 7.22 (m, 1H), 6.82 – 6.76 (m, 2H), 6.63 – 6.62 (m, 1H), 5.89

(br, 2H); $^{13}C\{^{1}H\}$NMR ($CDCl_3$, 100 MHz, ppm): δ = 163.9, 155.7, 147.1, 145.6, 139.5, 132.6, 127.8, 116.8, 116.2, 113.9, 112.1, 105.3.

2-(5-(Thiophen-2-yl)-1,3,4-oxadiazol-2-yl)aniline **(3ak)** [12]

The title compound was prepared according to the general working procedure and purified by column chromatography (petroleum ether / ethyl acetate = 8:1) to give the product as a light yellow solid: 69% yield, (50 mg); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.82 − 7.79 (m, 2H), 7.56 − 7.54 (m, 1H), 7.28 − 7.17 (m, 2H), 6.80 – 6.75 (m, 2H), 5.87 (br, 2H); $^{13}C\{^{1}H\}$NMR ($CDCl_3$, 100 MHz, ppm): δ = 164.0, 159.0, 147.0, 132.5, 130.0, 129.6, 128.1, 127.7, 125.2, 116.7, 116.1, 105.4.

2,2'-(1,3,4-Oxadiazole-2,5-diyl)dianiline **(3al)** [12]

The title compound was prepared according to the general working procedure and purified by column chromatography (petroleum ether / ethyl acetate = 6:1) to give the product as a light yellow solid: 46% yield, (35 mg); ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ = 7.89 − 7.86 (m, 2H), 7.31 − 7.26 (m, 2H), 6.93 – 6.91 (m, 2H), 6.77 (br, 4H), 6.73 – 6.69 (m, 2H); $^{13}C\{^{1}H\}$NMR (DMSO-d_6, 100 MHz, ppm): δ = 162.8, 148.3, 132.9, 128.3, 116.3, 116.1, 104.5.

2-(5-(4-Aminophenyl)-1,3,4-oxadiazol-2-yl)aniline **(3am)**

The title compound was prepared according to the general working procedure and purified by column chromatography (petroleum ether / ethyl acetate = 2:1) to give the product as a light yellow solid: 70% yield, (53 mg); ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ = 7.81 − 7.77 (m, 3H), 7.27 − 7.23 (m, 1H), 6.91 – 6.89 (m, 1H), 6.73 – 6.67 (m, 5H), 5.95 (br, 2H); $^{13}C\{^{1}H\}$NMR (DMSO-d_6, 100 MHz, ppm): δ = 163.5, 163.3, 152.8, 148.0, 132.5, 128.7, 127.9, 116.3, 116.0, 114.1, 110.1, 105.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{13}N_4O$ 253.1084; Found: 253.1091.

2-(5-Methyl-1,3,4-oxadiazol-2-yl)aniline **(3ao)** [12]

The title compound was prepared according to the general working procedure and purified by column chromatography (petroleum ether / ethyl acetate = 6:1) to give the product as a light yellow solid: 57% yield, (30 mg); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.72 (dd, J = 6.4 Hz, 1H), 7.28 −

7.24 (m, 1H), 6.81 – 6.73 (m, 2H), 5.83 (br, 2H), 2.62 (s, 3H); $^{13}C\{^{1}H\}$NMR ($CDCl_3$, 100 MHz, ppm): δ = 164.9, 161.8, 146.8, 132.3, 127.7, 116.7, 116.1, 105.9, 10.9.

2-(5-Propyl-1,3,4-oxadiazol-2-yl)aniline **(3ap)** [13]

The title compound was prepared according to the general working procedure and purified by column chromatography (petroleum ether / ethyl acetate = 8:1) to give the product as a light yellow solid: 51% yield, (31 mg); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.74 (d, J = 8.0 Hz, 1H), 7.29 − 7.25 (m, 1H), 6.82 – 6.74 (m, 2H), 5.85 (br, 2H), 2.92 (t, J = 7.6 Hz, 2H), 1.95 – 1.86 (m, 2H), 1.08 (t, J = 7.6 Hz, 3H); $^{13}C\{^{1}H\}$NMR ($CDCl_3$, 100 MHz, ppm): δ = 165.0, 164.7, 146.8, 132.2, 127.7, 116.7, 116.1, 106.0, 27.1, 20.1, 13.6.

4-Methyl-2-(5-phenyl-1,3,4-oxadiazol-2-yl)aniline **(3ba)** [12]

The title compound was prepared according to the general working procedure and purified by column chromatography (petroleum ether / ethyl acetate = 10:1) to give the product as a light yellow solid: 74% yield, (56 mg); ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ = 8.15 – 8.13 (m, 2H), 7.68 (s, 1H), 7.64 − 7.62 (m, 3H), 7.13 − 7.10 (m, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.61 (br, 2H), 2.25 (s, 3H); $^{13}C\{^{1}H\}$NMR ($CDCl_3$, 100 MHz, ppm): δ = 164.6, 162.7, 144.9, 133.6, 131.6, 129.0, 127.5, 126.9, 126.0, 123.9, 116.4, 105.6, 20.3.

4-Fluoro-2-(5-phenyl-1,3,4-oxadiazol-2-yl)aniline **(3ca)** [12]

The title compound was prepared according to the general working procedure and purified by column chromatography (petroleum ether / ethyl acetate = 10:1) to give the product as a light yellow solid: 63% yield, (55 mg); ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ = 8.18 (d, J = 8.4 Hz, 2H), 7.71 − 7.61 (m, 4H), 7.23 − 7.18 (m, 1H), 6.96 – 6.92 (m, 1H), 6.69 (br, 2H); $^{13}C\{^{1}H\}$NMR (DMSO-d_6, 100 MHz, ppm): δ = 164.0, 162.8, 153.6 (d, J = 229.9 Hz), 145.2, 132.5, 129.8, 127.3, 123.7, 120.8 (d, J = 23.1 Hz), 117.9 (d, J = 7.3 Hz), 113.2 (d, J = 24.2 Hz), 104.1 (d, J = 8.0 Hz).

4-Chloro-2-(5-phenyl-1,3,4-oxadiazol-2-yl)aniline **(3da)** [12]

The title compound was prepared according to the general working procedure and purified by column chromatography (petroleum ether / ethyl acetate = 10:1) to give the product as a light yellow solid: 69% yield, (56 mg); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.20 – 8.17 (m, 2H), 7.90 − 7.89 (m, 1H), 7.65 − 7.61 (m, 3H), 7.33 − 7.30 (m, 1H), 6.96 (d, J = 8.9 Hz, 1H), 6.92 (br, 2H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz, ppm): δ = 163.6, 163.0, 145.6, 132.4, 131.9, 129.1, 127.0, 126.9, 123.5, 121.3, 117.6, 106.6.

4-Bromo-2-(5-phenyl-1,3,4-oxadiazol-2-yl)aniline **(3ea)** [12]

The title compound was prepared according to the general working procedure and purified by column chromatography (petroleum ether / ethyl acetate = 10:1) to give the product as a light yellow solid: 70% yield, (66 mg); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.16 – 8.12 (m, 2H), 7.95 − 7.94 (m, 1H), 7.57 − 7.52 (m, 3H), 7.34 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.94 (br, 2H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz, ppm): δ = 163.4, 163.0, 146.0, 135.1, 131.9, 129.8, 129.1, 127.0, 123.5, 117.9, 107.9, 107.1.

5-Chloro-2-(5-phenyl-1,3,4-oxadiazol-2-yl)aniline **(3fa)**

The title compound was prepared according to the general working procedure and purified by column chromatography (petroleum ether / ethyl acetate = 10:1) to give the product as a light yellow solid: 75% yield, (61 mg); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.14 – 8.10 (m, 2H), 7.76 (d, J = 8.5 Hz, 1H), 7.56 − 7.50 (m, 3H), 6.82 – 6.81 (m, 1H), 6.76 – 6.74 (m, 1H), 6.00 (br, 2H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz, ppm): δ = 163.9, 162.8, 147.8, 138.4, 131.8, 129.1, 128.9, 126.9, 123.6, 117.2, 115.6, 104.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{11}N_3OCl$ 272.0591; Found: 272.0591.

5-Methoxy-2-(5-phenyl-1,3,4-oxadiazol-2-yl)aniline **(3ga)**

The title compound was prepared according to the general working procedure and purified by column chromatography (petroleum ether / ethyl acetate = 6:1) to give the product as a light yellow solid: 71% yield, (57 mg); ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ = 8.13 – 8.10 (m, 2H), 7.78 (d, J = 8.8 Hz, 1H), 7.64 − 7.60 (m, 3H), 6.80 (br, 2H), 6.46 – 6.45 (m, 1H), 6.35 – 6.33 (m, 1H), 3.77

(s, 3H); $^{13}C\{^{1}H\}$NMR ($CDCl_3$, 100 MHz, ppm): δ = 164.6, 163.1, 162.2, 148.8, 131.4, 129.4, 129.0, 126.8, 124.0, 105.0, 99.6, 99.5, 55.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{14}N_3O_2$ 268.1086; Found: 268.1088.

2-Chloro-6-(5-phenyl-1,3,4-oxadiazol-2-yl)aniline **(3ha)** [12]

The title compound was prepared according to the general working procedure and purified by column chromatography (petroleum ether / ethyl acetate = 20:1) to give the product as a light yellow solid: 66% yield, (54 mg); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 8.15 – 8.10 (m, 2H), 7.81 − 7.79 (m, 1H), 7.59 − 7.51 (m, 3H), 7.42 − 7.40 (m, 1H), 6.74 (t, J = 7.9 Hz, 1H), 6.44 (br, 2H); $^{13}C\{^{1}H\}$NMR ($CDCl_3$, 100 MHz, ppm): δ = 164.0, 163.0, 143.4, 132.2, 131.8, 129.1, 126.9, 126.4, 123.6, 120.0, 116.5, 106.8.

2,4-Dimethyl-6-(5-phenyl-1,3,4-oxadiazol-2-yl)aniline **(3ia)**

The title compound was prepared according to the general working procedure and purified by column chromatography (petroleum ether / ethyl acetate = 10:1) to give the product as a light yellow solid: 61% yield, (48 mg); ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ = 8.16 – 8.12 (m, 2H), 7.65 − 7.61 (m, 3H), 7.57 (s, 1H), 7.04 (s, 1H), 6.42 (br, 2H), 2.23 (s, 3H), 2.16 (s, 3H); $^{13}C\{^{1}H\}$NMR ($CDCl_3$, 100 MHz, ppm): δ = 165.0, 162.6, 143.3, 134.6, 131.5, 129.0, 126.9, 125.6, 125.4, 123.9, 123.1, 105.3,20.3,17.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{16}N_3O$ 266.1298; Found: 266.1298.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS:

We are grateful to the Talent Project of Fuyang Normal University (No. 2019kyqd0017).

Supporting Information

^{1}H NMR and ^{13}C NMR spectra for all the products; This material is available free of charge via the Internet at http://pubs.acs.org.

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