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A Multicomponent Electrosynthesis of 1,5-Disubstituted and 1-Aryl 1,2,4-Triazoles

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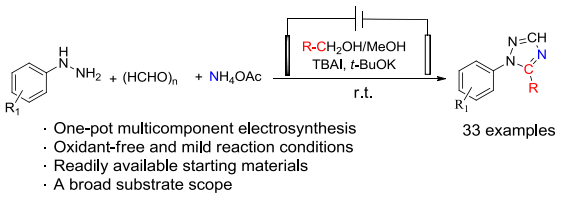
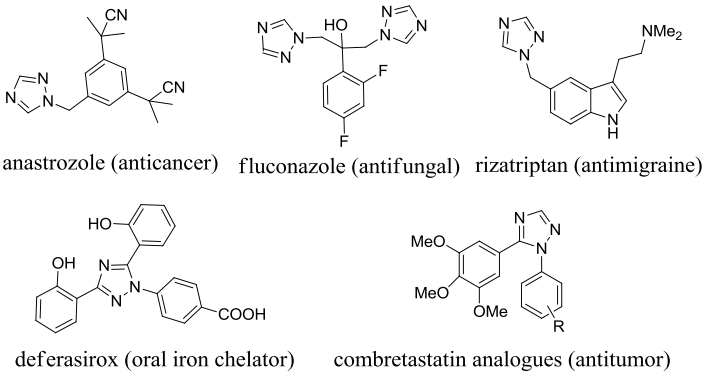


ABSTRACT: A novel electrochemical route has been developed for the synthesis of 1,5-disubstituted and 1-aryl 1,2,4-triazoles from aryl hydrazines, paraformaldehyde, NH_4OAc and alcohols. In this multicomponent reaction system, alcohols act as solvents as well as reactants and NH_4OAc is used as the nitrogen source. With the assistance of reactive iodide radical or I_2 and NH_3 electrogenerated in situ, this process could effectively avoid the use of strong oxidants and transition-metal catalysts and be smoothly carried out at room temperature to give a wide array of 1,2,4-triazole derivatives in good to high yields. Preliminary studies reveal that the reaction mechanism involves a radical process.

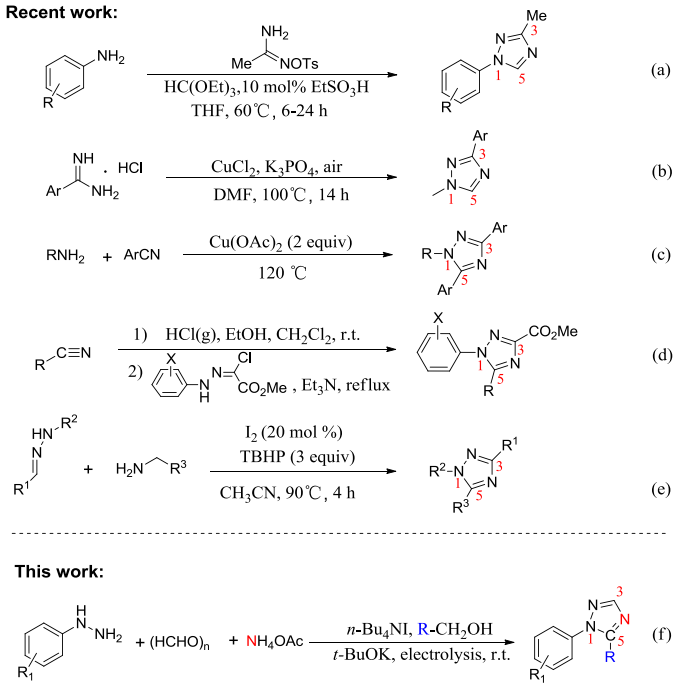
Introduction

1,2,4-Triazoles are important skeletons in numerous agrochemicals, pharmaceuticals, biological active compounds. A lot of compounds containing 1,2,4-triazole motif such as 1,3,5-trisubstituted and 1,5-disubstituted 1,2,4-triazoles display good anticancer, antifungal, antibacterial and anti-inflammatory activities (Scheme 1).[1] Over the past decades, much effort has been devoted to the synthesis of substituted 1,2,4-triazoles and many synthetic methods have been reported.[2–4] But some drawbacks, such as elevated temperatures, limited substrate scope, inconvenient starting materials or multi-step processes, still exist in some synthetic routes. In addition, the classic C-N coupling reactions to prepare aryl-1,2,4-triazoles inevitably generated regio isomeric triazole mixtures. Recently some novel synthetic methods have been developed for the preparation of specific location substituted 1,2,4-triazoles, such as the transformation from anilines, amino pyridines, and pyrimidines (Scheme 2a),[5] the copper-catalyzed reaction of amidines with solvent DMF in the presence of base and oxidant (Scheme 2b),[6] copper-mediated cyclization reaction of amine with nitriles (Scheme 2c),[7] the reaction of nitriles with hydrazonoyl chlorides through a two-step process (Scheme 2d)[8] and I_2-catalyzed oxidative coupling reactions of hydrazones and amines (Scheme 2e).[9] Although much progress has been made in the synthesis of multi-substituted 1,2,4-triazoles, it is still desirable to develop a simple and efficient method for the synthesis of specific location substituted 1,2,4-triazoles.

Scheme 1. Some Bioactive 1,2,4-Triazole Derivatives



Scheme 2. Different Methods for Synthesis of Specific Location Substituted 1,2,4-Triazoles



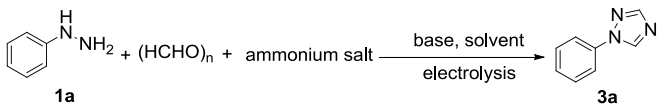
An electrochemical method has attracted more and more attention in organic synthesis since electrons can act as clean and safe redox reagents to replace expensive or hazardous chemicals. Recently, advances in synthetic organic electrochemistry have been extensively reviewed.[10] Among various electrochemical strategies, reactive iodide radical or iodine electrogenerated in situ at an anode could effectively induce or catalyze some transformations,[11] which seems to be attractive. With the help of I_2 electrogenerated *in situ* at a graphite anode, our group has also achieved the electrochemical conversion of CO_2 with olefins or aryl hydrazines and paraformaldehyde.[12] These successful electrosynthetic examples motivate us to develop a new electrochemical route for the synthesis of substituted 1,2,4-triazoles under mild conditions. Herein, we report an interesting one-pot multicomponent electrochemical route to synthesize

1,5-disubstituted and 1-aryl substituted 1,2,4-triazoles from aryl hydrazines, paraformaldehyde, NH_4OAc and alcohols (Scheme 2f). Although the electrochemical basic principle is similar to that in the previous investigations, this synthetic route is novel for the preparation of substituted 1,2,4-triazoles. Differing from the previous work,[5–9] the present work uses NH_4^+ as the nitrogen source, which further broadens a synthetic scope of 1,2,4-triazole derivatives. With the assistance of electrochemical oxidation and electrocatalysis, this synthetic route effectively avoids the direct use of hazardous oxidants and transition-metal catalysts.

Results and Discussion

In this work we chose phenylhydrazine **1a**, paraformaldehyde and ammonium acetate as model substrates to start our investigation. To optimize the electrolytic conditions, the electrolysis was carried out with constant current in an undivided cell equipped with a graphite rod anode and a Ni plate cathode. With methanol as the solvent and NaI as the mediator, the desired product 1-phenyl-1*H*-1,2,4-triazole **3a** was obtained in 62% yield after the electrolysis for 6 h (Table 1, entry 1). Encouraged by this result, we replaced NaI with KI, NH_4I, *n*-Bu_4NI (TBAI), and *n*-Bu_4NBr (TBABr) to further examine this reaction (Table 1, entries 2–5). It was found that TBAI gave the best result with 82% isolated yield of **3a**. Solvent was also a key parameter. When MeCN, DMF or DMSO was used as the solvent, only a trace amount of **3a** was detected (Table 1, entries 6–8). In addition, we further examined the effect of ammonium salts. Using $(NH_4)_2CO_3$ or NH_4Cl as the nitrogen source, the electrolytic results became unsatisfied (Table 1, entries 9 and 11). Especially in the NH_4HCO_3 case, only a small amount of **3a** was obtained (Table 1, entry 10). Moreover, studies on bases indicated that strong base was more favorable to this reaction. For example, NaOH and *t*-BuOK afforded the target product **3a** in higher yields than weak bases (Table 1, entries 12–15). According to our experience, I_2 electrogenerated *in situ* at an anode could promote some transformations effectively.[12] In the absence of any iodides, only a trace amount of **3a** was observed (Table 1, entry 16), indirectly indicating that reactive iodine electrogenerated *in situ* could promote this transformation as well. When NH_4I was used as the sole nitrogen source without NH_4OAc, a byproduct iodobenzene was obviously increased so that the yield of **3a** declined to 49% (Table 1, entry 17). Thus, NH_4OAc as the nitrogen source is necessary.

Table 1. Optimization of Reaction Conditions [a]



Entry	Solvent	Mediator	Ammonium Salt	Base	Yield [b](%)
1	MeOH	NaI	NH_4OAc	*t*-BuOK	62
2	MeOH	KI	NH_4OAc	*t*-BuOK	71
3	MeOH	NH_4I	NH_4OAc	*t*-BuOK	78
4	MeOH	TBAI	NH_4OAc	*t*-BuOK	89(82)[c]
5	MeOH	TBABr	NH_4OAc	*t*-BuOK	22
6	MeCN	TBAI	NH_4OAc	*t*-BuOK	trace
7	DMF	TBAI	NH_4OAc	*t*-BuOK	trace

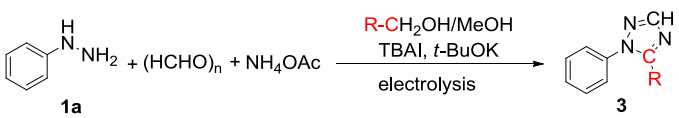
8	DMSO	TBAI	NH_4OAc	*t*-BuOK	trace
9	MeOH	TBAI	$(NH_4)_2CO_3$	*t*-BuOK	21
10	MeOH	TBAI	NH_4HCO_3	*t*-BuOK	12
11	MeOH	TBAI	NH_4Cl	*t*-BuOK	35
12	MeOH	TBAI	NH_4OAc	NaOH	77
13	MeOH	TBAI	NH_4OAc	DBU	49
14	MeOH	TBAI	NH_4OAc	K_2CO_3	19
15	MeOH	TBAI	NH_4OAc	Cs_2CO_3	15
16	MeOH	–	NH_4OAc	*t*-BuOK	trace[d]
17	MeOH	NH_4I[e]	–	*t*-BuOK	49

[a] Reaction conditions: phenylhydrazine **1a** (1.0mmol), paraformaldehyde (1.5 mmol), ammonium salt (4.0 mmol), mediator (0.5 equiv.), base (2.0 equiv.), solvent (20 mL), undivided cell, a graphite rod as the anode and a Ni plate as the cathode, room temperature, current 55 mA and 6 h. [b] Yield was analyzed by GC-MS with *n*-dodecane as an internal standard. [c] Isolated yield. [d] *n*-Bu_4NBF_4 (1.0 equiv.) was used as the supporting electrolyte. [e] NH_4I (4 equiv.).

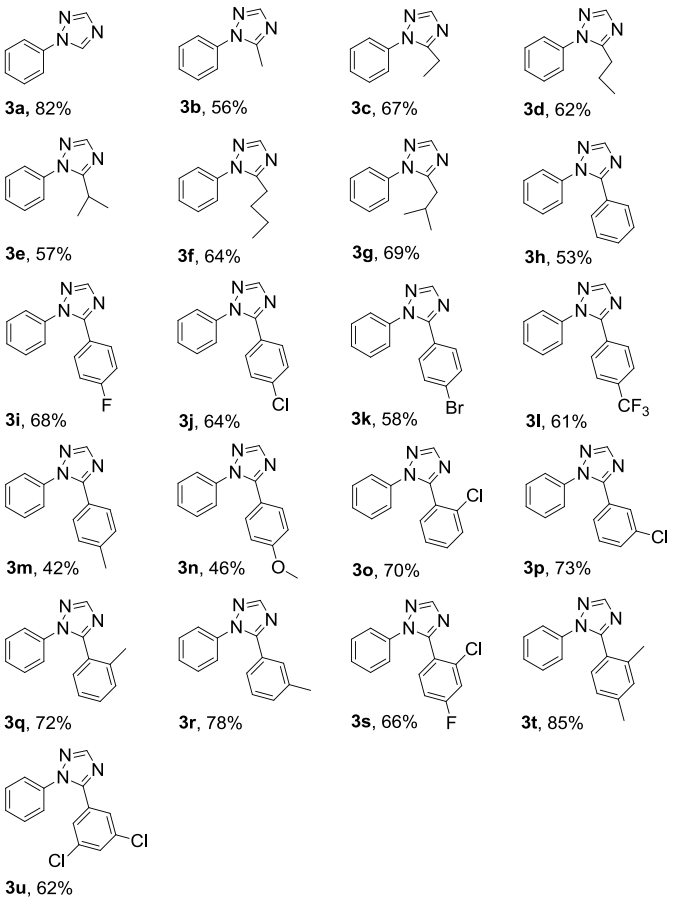
When ethanol was used as the solvent, we found that the main product was 5-methyl-1-phenyl-1*H*-1,2,4-triazole (Table 2, **3b**). This interesting result (1,5-disubstituted 1,2,4-triazole product) encouraged us to examine the electrolytic results with various alcohols. When 1-propanol, butanol, isobutanol, pentanol or isopentanol was used the solvent respectively, the corresponding 1,5-disubstituted 1,2,4-triazole products were successfully obtained in good yields as well (Table 2, **3c**–**3g**). These results indicated that the solvent alcohols took part in the reaction to result in the formation of 1,5-disubstituted 1,2,4-triazoles. In the present case, the alcohols play a dual role, solvents and reactants. Notably, no corresponding product was obtained with 2-propanol or 2-butyl alcohol as the substrate. So we deduced that the oxidation of alcohols to aldehydes might be one of key steps in the formation of 1,5-disubstituted of 1,2,4-triazoles.

It should be pointed out that the electrical conductivity was very poor when benzyl alcohols were used as solvents. In order to make sure that the electrosynthesis could be performed smoothly, we used the mixture of various benzyl alcohols (10 equiv.) with MeOH (20 mL) as the solvent to further examine the electrolysis. It was found that the benzyl alcohols bearing with various groups could give the target products in moderate to good yields (Table 2, **3h**–**3u**). Moreover, the benzyl alcohols with chloro or methyl substituted group on the *ortho*- or *meta*-position displayed higher reactivity than those on the *para*-position (Table 2, **3o**, **3p** and **3j**; or **3q**, **3r** and **3m**). Multi-substituted benzyl alcohols could be also transformed to corresponding 1,2,4- triazoles smoothly (Table 2 **3s**, **3t** and **3u**). These experimental results demonstrated that this electrochemical route was applicable to both aliphatic alcohols and benzyl alcohols.

Table 2. Electrolytic Results of Various Alcohols [a,b]



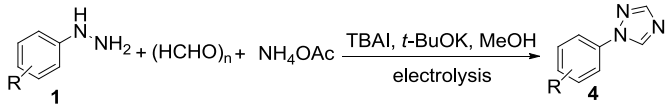
1a **3**

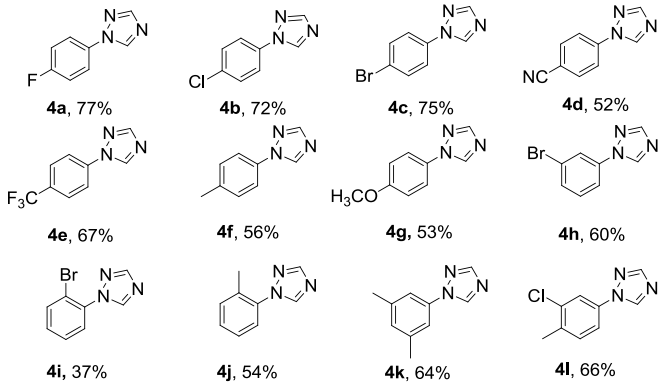


[a] Reaction conditions: phenylhydrazine (1.0 mmol) paraformaldehyde (1.0 mmol), NH_4OAc (4.0 mmol), TBAI (0.5 equiv.), *n*-Bu_4NBF_4 (2 equiv.), aliphatic alcohol (20 mL) or benzyl alcohols (10 equiv.)/MeOH (20 mL), *t*-BuOK (2.0 equiv.), undivided cell, a graphite rod as the anode and a Ni plate as the cathode, room temperature, current 55 mA and 6 h. [b] Isolated yield.

With methanol used as the solvent, we further examined the scope and generality of phenylhydrazines. As shown in Table 3, various substituted phenylhydrazines could afford the corresponding products in moderate to high yields. This process could tolerate a lot of functional groups (Table 3, **4a**–**4l**). In general, electron-withdrawing groups were more favorable to the reaction than electron-donating ones in the same substituted position. In addition, phenylhydrazine derivatives with bromo substituted on the *para*- and *meta*-position showed higher reactivity than those on the *ortho*-position (Table 3, **4c**, **4h** and **4i**). This electrochemical method was also applicable to poly-substituted phenylhydrazine derivatives (Table 3, **4k** and **4l).** However, the yields of the target products are not more than 90%, which may be due to a side reaction of aryl hydrazines with I_2 to form iodobenzene derivatives. The side product iodobenzene was observed in our experiments.

Table 3. Scope of Phenylhydrazine Derivatives[a,b]

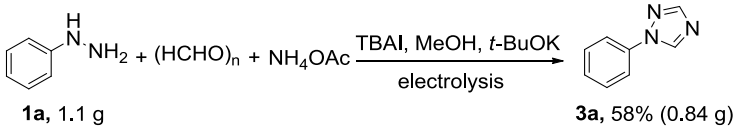




[a] Reaction conditions: phenylhydrazine derivatives **1** (1.0 mmol), paraformaldehyde (1.5 mmol), NH_4OAc (4.0 mmol), TBAI (0.5 equiv.), MeOH (20 mL), *t*-BuOK (2.0 equiv.), undivided cell, a graphite rod as the anode and a Ni plate as the cathode, room temperature, current 55 mA and 6 h. [b] Isolated yield.

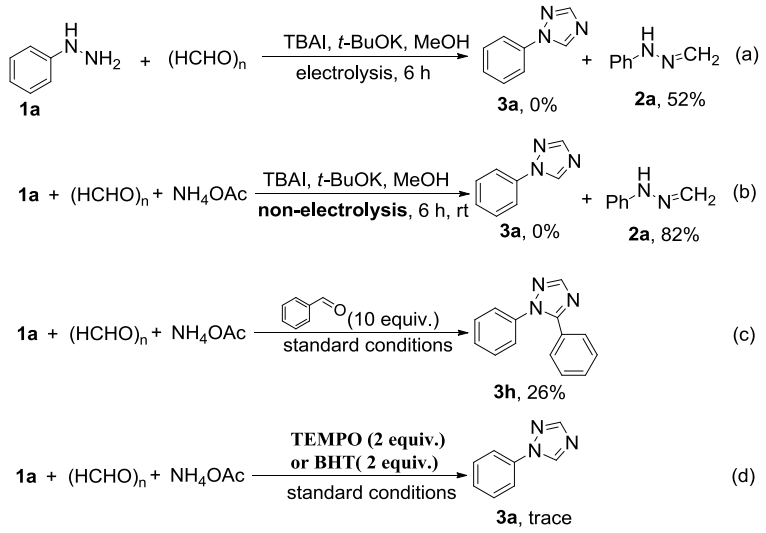
In order to demonstrate the potential practical applications of this electrochemical route, the electrosynthesis was carried out on a gram scale. As shown in Scheme 3, when 1.1 g of **1a** was used under the standard conditions, the product **3a** was obtained in 58% isolated yield with the electrolysis prolonged to 10 h, indicating that this electrochemical route could be scaled up to a preparing scale.

Scheme 3. Gram-Scale Experiment



Several control experiments were conducted to explore the reaction mechanism. In the absence of ammonium salt, **2a** was obtained instead of **3a** (Scheme 4a), which showed that ammonium salt was essential for the formation of 1,2,4-triazoles and **2a** was likely to be an intermediate for this electrosynthesis. **3a** was not obtained under the non-electrolysis conditions (Scheme 4b), indirectly demonstrating that the reactive iodine and NH_3 electrogenerated *in situ* played very important roles. Under the standard conditions, **3h** was also obtained in 26% yield with benzaldehyde as the substrate (Scheme 4c), suggesting that the alcohols might be oxidized to aldehyde in this electrosynthesis. When a radical inhibitor 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-tert-butyl-4-methylphenol (BHT) was added to the electrolytic system (Scheme 4d), the electrosynthesis was inhibited, which indicated that the reaction might involve a radical pathway.

Scheme 4. Control Experiments



Cyclic voltammetry (CV) experiments were further carried out to gain insight into the reaction mechanism. In the blank experiment (Figure 1-Ⅰ, curve a), the peak that supposed to be the oxidation peak of MeOH at 1.3 V *vs*. SCE was very weak, demonstrating that MeOH could not be easily electro-oxidized to HCHO in the present conditions. For phenylhydrazine **1a** and paraformaldehyde (Figure 1-Ⅰ, curve b and c), oxidation peaks were hardly observed, indicating that the electrochemical oxidation of phenylhydrazine or paraformaldehyde could be neglected. However, an obvious oxidation peak was observed at 1.0 V *vs*. SCE in the presence of **1a** and paraformaldehyde at the same time (Figure 1-Ⅰ, curve e). This peak was attributed to the oxidation of intermediate 1-methylene-2-phenylhydrazine (**2a**) since phenylhydrazine could easily react with paraformaldehyde to form **2a** at room temperature (Scheme 4b). In the alone *n*-Bu_4NI case (Figure 1-Ⅱ, curve d), a very strong oxidation peak occurred at 1.4 V *vs*. SCE, which was due to the electro-oxidation of I^- ions. Under the similar electrosynthetic conditions (Figure 1-Ⅰ, curve f), the oxidation peak current at 1.0 V *vs.* SCE belonging to the oxidation of the intermediate **2a** was quite obvious. According to these CV results, it could be concluded that the electrochemical oxidation of I^- ions at an anode was a main process and the electro-oxidation of **2a** also should be considered in the present electrosynthetic system. In addition, it could be deduced that alcohols were converted to aldehydes through the chemical oxidations instead of electrochemical oxidations.

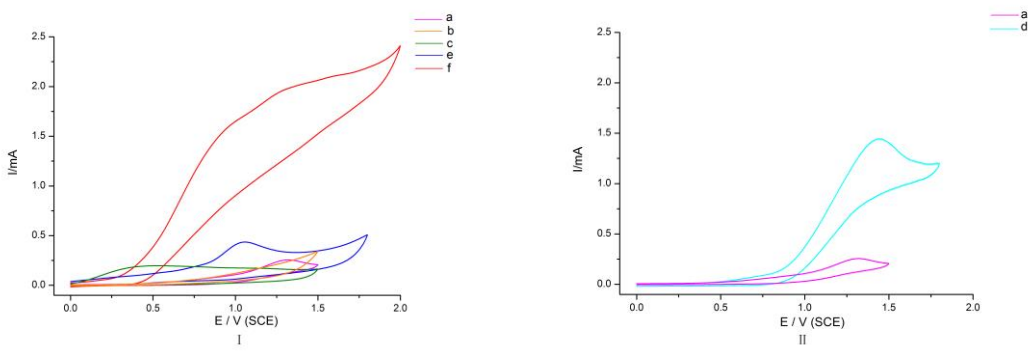
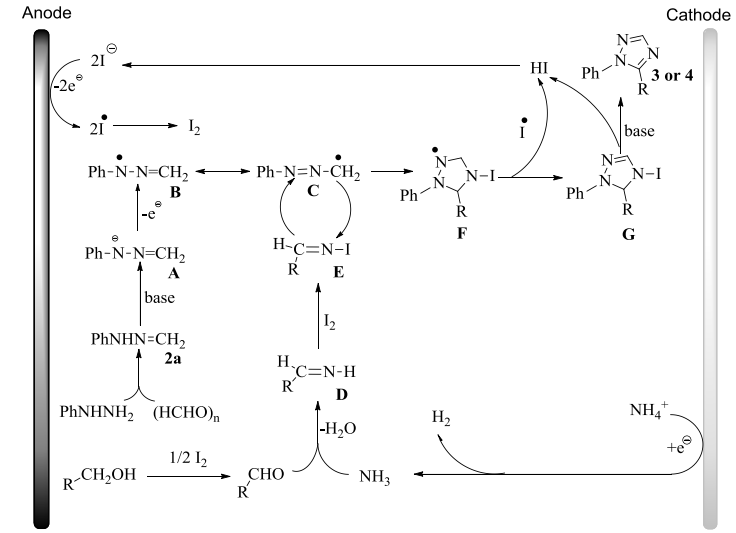


Figure 1. Cyclic voltammograms of 0.1 mol L^{-1} of *n*-Bu_4NBF_4-MeOH (20 mL)-*t*-BuOK (2.0 mmol) solution containing different compounds: (a) blank experiment; (b) only phenylhydrazine **1a** (1.0 mmol); (c) only paraformaldehyde (1.5 mmol); (d) only *n*-Bu_4NI (0.5 mmol); (e) phenylhydrazine **1a** (1.0 mmol) and paraformaldehyde (1.5 mmol); (f) phenylhydrazine **1a** (1.0 mmol), paraformaldehyde (1.5 mmol), NH_4OAc (4.0 mmol) and *n*-Bu_4NI (0.5 mmol); with a GC disk working electrode, Pt counter electrode and SCE reference electrode at 100 mV/s scan rate.

Based on the above experiments and the previous investigations,[11−16] a plausible reaction mechanism was outlined in Scheme 5. Initially, I^- ions are electro-oxidized at the anode to form a reactive iodide radical or I_2.[11a,12] At the same time, phenylhydrazine easily reacts with paraformaldehyde to produce intermediate 1-methylene-2-phenylhydrazine **2a**. In the presence of a strong base, **2a** can generate 1-methylene-2-phenylhydrazine anion **A,**[13,14] followed by the electrochemical oxidation to yield a radical **B,** which is supported by the CV experiments. Then the radical **B** can be converted to a resonance structural radical **C**.[11c] On the other hand, the alcohol can be chemically oxidized to aldehyde at room temperature with the help of I_2 electrogenerated at the anode.[15] Subsequently, the aldehyde reacts with NH_3 resulting from the electroreduction of NH_4^+ ions at the cathode to form aldimine intermediate **D**, followed by the reaction with I_2 to generate an *N*-iodo aldimine intermediate **E**.[16] The intermolecular radical cycloaddition of radical **C** with **E** forms a radical **F**. The deprotonation of the radical **F** by an iodide radical gives intermediate **G.** Finally, aromatization of **G** by eliminating HI generates substituted 1,2,4-triazole **3** or **4**. Moreover, the regenerated I^- ions can join to the next reaction cycle.

Scheme 5. Possible Mechanism



Conclusions

In summary, we have developed a facile electrochemical protocol for the synthesis of 1,5-disubstituted and 1-aryl 1,2,4-triazoles from aryl hydrazines, paraformaldehyde, NH_4OAc and alcohols in an undivided cell. This one-pot multicomponent electrosynthetic route has a potential application in pharmaceutical synthesis due to its low toxic solvent, mild reaction conditions, simplicity, readily available starting materials and a broad substrate scope.

EXPERIMENTAL SECTION

General Information: Solvents and reagents were commercially available and used as received without further treatment. Reactions were monitored by thin-layer chromatography (TLC). ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker DRX-400 spectrometer with $CDCl_3$ or (d_6-DMSO) as a solvent and TMS as an internal standard. The chemical shifts are referenced to signals at 7.26 (or 2.5) and 77.23 (or 39.51) ppm, respectively. Mass spectra were recorded on a Thermo Scientific ISQ gas chromatograph-mass spectrometer. The data of HRMS was carried out on a high-resolution mass spectrometer (LCMS-IT-TOF). Melting points were determined with a Büchi Melting Point B-545 instrument.

General Procedure for the Electrosynthesis of Substituted 1,2,4-Triazoles: In a typical procedure, phenylhydrazine **1a** (1.0 mmol), paraformaldehyde (1.5 mmol), NH_4OAc (4.0 mmol), *t*-BuOK (2.0 equiv.) and TBAI (0.5 equiv.) were dissolved in a Teflon cup (50 mL) containing 20 mL of MeOH. The Teflon cup was placed in a stainless-steel cell equipped with a graphite rod (d=0.4 cm, L=1 cm) anode and a Ni plate (area 2 cm^2) cathode connecting to a DC regulated power supply. The electrosythesis was carried out with current 55 mA at room temperature for 6 h. After the electrolysis, the saturated aqueous $Na_2S_2O_3$ solution (10 mL) was added to the electrolyte solution and the mixture was extracted with ethyl acetate (3×15 mL). The combined organic layer was dried over anhydrous $MgSO_4$. The solvent was removed under vacuum. The crude product was purified by flash chromatography on silica gel using a mixture of petroleum ether and ethyl acetate (100:1) to give the pure target product.

Phenyl-1H-1,2,4-triazole ***3a***.[3b] 118.6 mg, 82% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.55 (s, 1H), 8.08 (s, 1H), 7.64 (d, J = 8.0 Hz, 2H), 7.47 (t, J = 7.8 Hz, 2H), 7.36 (t, J = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 152.7, 141.1, 137.1, 129.9, 128.3, 120.2.

5-Methyl-1-phenyl-1H-1,2,4-triazole ***3b*****.** 88.5 mg, 56% yield, brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.91 (s, 1H), 7.52 – 7.47 (m, 2H), 7.43 (dd, J = 7.0, 4.0 Hz, 3H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 152.2, 151.1, 137.6, 129.6, 128.9, 124.8, 13.3; HRMS (ESI, m/z): Calcd. for $C_9H_{10}N_3$ $[M+H]^+$ 160.0869; found 160.0865.

5-Ethyl-1-phenyl-1H-1,2,4-triazole ***3c***. 116.4 mg, 67% yield, brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.94 (s, 1H), 7.52 – 7.40 (m, 5H), 2.81 (q, J = 7.5 Hz, 2H), 1.32 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 157.1, 151.2, 137.6, 129.6, 129.1, 125.2, 20.3, 12.2; HRMS (ESI, m/z): Calcd. for $C_{10}H_{12}N_3$ $[M+H]^+$ 174.1026; found 174.1020.

1-Phenyl-5-propyl-1H-1,2,4-triazole ***3d***. 115.8 mg, 62% yield, brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.94 (s, 1H), 7.49 (dt, J = 13.0, 6.7 Hz, 3H), 7.41 (d, J = 7.5 Hz, 2H), 2.76 (t, J = 7.6 Hz, 2H), 1.78 (dd, J = 15.0, 7.5 Hz, 2H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 156.2, 151.2, 137.7, 129.6, 129.2, 125.4, 28.5, 21.3, 13.9; HRMS (ESI, m/z): Calcd. for $C_{11}H_{14}N_3$ $[M+H]^+$ 188.1182; found 188.1177.

5-Isopropyl-1-phenyl-1H-1,2,4-triazole ***3e*****.** 105.9 mg, 57% yield, brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.94 (s, 1H), 7.51 – 7.46 (m, 3H), 7.39 (dd, J = 8.0, 1.4 Hz, 2H), 3.14 (dt, J = 13.7, 6.8 Hz, 1H), 1.30 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 161.1, 151.2, 137.6, 129.7, 129.3, 125.7, 25.9, 21.8; HRMS (ESI, m/z): Calcd. for $C_{11}H_{14}N_3$ $[M+H]^+$ 188.1182; found 188.1179.

5-Butyl-1-phenyl-1H-1,2,4-triazole ***3f***. 128.3 mg, 64% yield, brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.94 (s, 1H), 7.48 (dd, J = 13.4, 7.0 Hz, 3H), 7.41 (d, J = 7.7 Hz, 2H), 2.78 (t, J = 7.7 Hz, 2H), 1.79 – 1.68 (m, 2H), 1.33 (dd, J = 14.9, 7.4 Hz, 2H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 156.3, 151.2, 137.7, 129.6, 129.2, 125.33, 30.0, 26.3, 22.4, 13.8; HRMS (ESI, m/z): Calcd. for $C_{12}H_{16}N_3$ $[M+H]^+$ 202.1339; found 202.1334.

5-Isobutyl-1-phenyl-1H-1,2,4-triazole ***3g*****.** 138.5 mg, 69% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.96 (s, 1H), 7.53 – 7.46 (m, 3H), 7.40 (d, J = 7.7 Hz, 2H), 2.67 (d, J = 7.2 Hz, 2H), 2.15 (dt, J = 13.6, 6.8 Hz, 1H), 0.90 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 155.7, 151.2, 137.7, 129.6, 129.3, 125.7, 35.3, 28.1, 22.5; HRMS (ESI, m/z): Calcd. for $C_{12}H_{16}N_3$ $[M+H]^+$ 202.1339; found 202.1343.

1,5-Diphenyl-1H-1,2,4-triazole ***3h*****.** 116.6 mg, 53% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.08 (s, 1H), 7.50 – 7.45 (m, 2H), 7.41 – 7.28 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 154.0, 151.7, 138.3, 130.1, 129.5, 129.0, 128.9, 128.7, 127.9, 125.5; HRMS (ESI, m/z): Calcd. for $C_{14}H_{12}N_3$ $[M+H]^+$ 222.1026; found 222.1027.

5-(4-Fluorophenyl)-1-phenyl-1H-1,2,4-triazole ***3i*****.** 162.1 mg, 68% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.05 (s, 1H), 7.44 (ddd, J = 17.8, 5.9, 2.4 Hz, 5H), 7.32 (dd, J = 6.6, 3.0 Hz, 2H), 7.00 (t, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 163.7 (d, J = 249.8 Hz), 153.1, 151.6, 138.2, 131.1(d, J = 8.6 Hz), 129.6, 129.2, 125.5, 124.1 (d, J = 3.4 Hz), 115.9 (d, J = 21.8 Hz); HRMS (ESI, m/z): Calcd. for $C_{14}H_{11}FN_3$ $[M+H]^+$ 240.0932; found 240.0934.

5-(4-Chlorophenyl)-1-phenyl-1H-1,2,4-triazole ***3j*****.** 163.9 mg, 64% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) δ 8.07 (s, 1H), 7.42 (dd, J = 6.1, 2.4 Hz, 5H), 7.35 – 7.27 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 153.0, 151.7, 138.1, 136.4, 130.3, 129.7, 129.3, 129.0, 126.4, 125.5; HRMS (ESI, m/z): Calcd. for $C_{14}H_{11}ClN_3$ $[M+H]^+$ 256.0636; found 256.0638.

5-(4-Bromophenyl)-1-phenyl-1H-1,2,4-triazole ***3k*****.** 173.6 mg, 58% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) δ 8.08 (s, 1H), 7.45 (dd, J = 13.2, 5.4 Hz, 5H), 7.35 (d, J = 8.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 153.1, 151.8, 138.1, 132.0, 130.5, 129.7, 129.4, 126.8, 125.5, 124.8; HRMS (ESI, m/z): Calcd. for $C_{14}H_{11}BrN_3$ $[M+H]^+$ 300.0131; found 300.0132.

1-Phenyl-5-(4-(trifluoromethyl)phenyl)-1H-1,2,4-triazole ***3l*****.** 176.8 mg, 61% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.10 (s, 1H), 7.59 (q, J = 8.6 Hz, 4H), 7.45 – 7.41 (m, 3H), 7.35 – 7.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 152.6, 151.9, 138.0, 132.0 (q, J = 32.6 Hz), 131.4, 129.8, 129.5, 129.3, 125.7 (q, J = 3.7 Hz), 125.6, 123.8 (q, J = 270.8 Hz); HRMS (ESI, m/z): Calcd. for $C_{15}H_{11}F_3N_3$ $[M+H]^+$ 290.0898; found 290.0901.

1-Phenyl-5-(p-tolyl)-1H-1,2,4-triazole ***3m*****.** 99.3 mg, 42% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.06 (s, 1H), 7.37 (dt, J = 8.3, 4.8 Hz, 7H), 7.12 (d, J = 8.0 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 154.1, 151.6, 140.4, 138.4, 129.5, 129.4, 129.0, 128.9, 125.5, 125.0, 21.5; HRMS (ESI, m/z): Calcd. for $C_{15}H_{14}N_3$ $[M+H]^+$ 236.1182; found 236.1184.

5-(4-Methoxyphenyl)-1-phenyl-1H-1,2,4-triazole ***3n*****.** 114.7 mg, 46% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.05 (s, 1H), 7.42 (d, J = 8.1 Hz, 5H), 7.37 – 7.33 (m, 2H), 6.84 (d, J = 8.7 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 161.1, 153.9, 151.6, 138.5, 130.5, 129.6, 129.0, 125.6, 120.2, 114.2, 55.5; HRMS (ESI, m/z): Calcd. for $C_{15}H_{14}N_3O$ $[M+H]^+$ 252.1131; found 252.1133.

5-(2-Chlorophenyl)-1-phenyl-1H-1,2,4-triazole ***3o*****.** 179.2 mg, 70% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.15 (s, 1H), 7.44 (d, J = 7.2 Hz, 1H), 7.38 (d, J = 3.7 Hz, 2H), 7.34 – 7.26 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 151.8, 151.7, 137.8, 134.0, 132.0, 131.7, 130.2, 129.3, 128.5, 128.51, 127.2, 123.8; HRMS (ESI, m/z): Calcd. for $C_{14}H_{11}ClN_3$ $[M+H]^+$ 256.0636; found 256.0636.

5-(3-Chlorophenyl)-1-phenyl-1H-1,2,4-triazole ***3p***. 185.8 mg, 73% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.10 (s, 1H), 7.58 (s, 1H), 7.44 (d, J = 2.9 Hz, 3H), 7.36 (s, 3H), 7.30 (d, J = 7.4 Hz, 1H), 7.24 (t, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 152.6, 151.7,

137.9, 134.8, 130.2, 129.9, 129.6, 129.6, 129.4, 129.1, 126.9, 125.5; HRMS (ESI, m/z): Calcd. for $C_{14}H_{11}ClN_3$ $[M+H]^+$ 256.0636; found 256.0633.

1-Phenyl-5-(o-tolyl)-1H-1,2,4-triazole ***3q*****.** 169.6 mg, 72% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.14 (s, 1H), 7.36 – 7.26 (m, 6H), 7.24 (d, J = 1.5 Hz, 1H), 7.19 (dd, J = 15.3, 7.7 Hz, 2H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 153.9, 151.6, 137.9, 137.6, 130.8, 130.3, 130.3, 129.2, 128.5, 128.2, 126.1, 123.7, 19.8; HRMS (ESI, m/z): Calcd. for $C_{15}H_{14}N_3$ $[M+H]^+$ 236.1182; found 236.1181.

1-Phenyl-5-(m-tolyl)-1H-1,2,4-triazole ***3r*****.** 182.9 mg, 78% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.07 (s, 1H), 7.41 – 7.32 (m, 6H), 7.16 (t, J = 5.3 Hz, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 154.1, 151.6, 138.6, 138.4, 130.9, 129.71, 129.4, 129.0, 128.5, 127.8, 126.0, 125.5, 21.4; HRMS (ESI, m/z): Calcd. for $C_{15}H_{14}N_3$ $[M+H]^+$ 236.1182; found 236.1185.

5-(2-Chloro-4-fluorophenyl)-1-phenyl-1H-1,2,4-triazole ***3s*****.** 179.8 mg, 66% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.17 (s, 1H), 7.46 (dd, J = 8.6, 5.9 Hz, 1H), 7.38 – 7.33 (m, 3H), 7.31 – 7.27 (m, 2H), 7.17 (dd, J = 8.4, 2.4 Hz, 1H), 7.08 (td, J = 8.2, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 163.7 (d, J = 252.9 Hz), 151.8, 151.0, 137.7, 135.3 (d, J = 10.6 Hz), 133.4 (d, J = 9.2 Hz), 129.4, 128.7, 124.8 (d, J = 3.7 Hz), 123.8, 117.9 (d, J = 24.8 Hz), 114.8 (d, J = 21.5 Hz); HRMS (ESI, m/z): Calcd. for $C_{14}H_{10}ClFN_3$ $[M+H]^+$ 274.0542; found 274.0542.

5-(2,4-Dimethylphenyl)-1-phenyl-1H-1,2,4-triazole ***3t.*** 211.2 mg, 85% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.13 (s, 1H), 7.38 – 7.26 (m, 5H), 7.14 (d, J = 7.8 Hz, 1H), 7.05 – 6.98 (m, 2H), 2.34 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 154.2, 151.6, 140.3, 138.1, 137.4, 131.6, 130.3, 129.3, 128.2, 126.9, 125.5, 123.8, 21.5, 19.8; HRMS (ESI, m/z): Calcd. for $C_{16}H_{16}N_3$ $[M+H]^+$ 250.1339; found 250.1340.

5-(3,5-Dichlorophenyl)-1-phenyl-1H-1,2,4-triazole ***3u.*** 179.0 mg, 62% yield, brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.10 (s, 1H), 7.48 (d, J = 3.8 Hz, 3H), 7.35 (dd, J = 9.3, 5.1 Hz, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 151.9, 151.5, 137.7, 135.5, 130.7, 130.2, 129.9, 129.8, 127.3, 125.6; HRMS (ESI, m/z): Calcd. for $C_{14}H_{10}Cl_2N_3$ $[M+H]^+$ 290.0246; found 290.0245.

1-(4-Fluorophenyl)-1H-1,2,4-triazole ***4a.*** 125.0 mg, 77% yield, brown solid, mp 68–70 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) δ 8.50 (s, 1H), 8.08 (s, 1H), 7.64 (dd, J = 9.0, 4.6 Hz, 2H), 7.19 (t, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 162.3 (d, J = 247.0 Hz), 152.9, 141.1, 133.5 (d, J = 5.3 Hz), 122.3 (d, J = 8.6 Hz), 116.9 (d, J = 23.0 Hz); HRMS (ESI, m/z): Calcd. for $C_8H_7FN_3$ $[M+H]^+$ 164.0619; found 164.0618.

1-(4-Chlorophenyl)-1H-1,2,4-triazole ***4b***.[3b] 129.7 mg, 72% yield, white solid, mp 118–120 ˚C; ^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) 9.31 (s, 1H), 8.25 (s, 1H), 7.89 (d, J = 8.9 Hz, 2H), 7.63 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, d_6-DMSO): δ (ppm) 152.5, 142.5, 135.6, 131.9, 129.7, 121.0.

1-(4-Bromophenyl)-1H-1,2,4-triazole ***4c***.[3b] 167.5 mg, 75% yield, yellow solid, mp 140–142 ˚C; ^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) 9.32 (s, 1H), 8.25 (s, 1H), 7.79 (dd, J = 33.9, 8.4 Hz, 4H); ^{13}C NMR (100 MHz, d_6-DMSO): δ (ppm) 152.5, 142.4, 136.0, 132.6, 121.3, 120.2.

4-(1H-1,2,4-Triazol-1-yl)benzonitrile ***4d.***[3b] 89.2 mg, 52% yield, brown solid, mp 155–157 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.68 (s, 1H), 8.12 (s, 1H), 7.83 (d, J = 10.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 153.4, 141.4, 140.1, 134.1, 120.2, 117.9, 111.9.

1-(4-(Trifluoromethyl)phenyl)-1H-1,2,4-triazole ***4e*****.** 143.3 mg, 67% yield, brown solid, mp

80–82 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.65 (s, 1H), 8.13 (s, 1H), 7.80 (dd, J = 26.4, 8.5 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 153.2, 139.6, 136.5, 130.4 (q, J = 33.1 Hz), 127.3 (q, J = 3.8 Hz), 123.7 (q, J =270.5 Hz), 120.1; HRMS (ESI, m/z): Calcd. for $C_9H_7F_3N_3$ $[M+H]^+$ 214.0587; found 214.0590.

1-(p-Tolyl)-1H-1,2,4-triazole ***4f.*** 88.6 mg, 56% yield, brown solid, mp 64–66 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.60 (s, 1H), 8.14 (s, 1H), 7.59 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 7.8 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 152.7, 141.3, 138.4, 135.0, 130.4, 120.2, 21.1; HRMS (ESI, m/z): Calcd. for $C_9H_{10}N_3$ $[M+H]^+$ 160.0869; found 160.0871.

1-(4-Methoxyphenyl)-1H-1,2,4-triazole ***4g***.[3b] 92.1 mg, 53% yield, brown solid, mp 94–96 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.44 (s, 1H), 8.03 (s, 1H), 7.52 (d, J = 8.6 Hz, 2H), 6.95 (d, J = 8.6 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 159.5, 152.5, 141.2, 130.6, 121.9, 114.9, 55.7.

1-(3-Bromophenyl)-1H-1,2,4-triazole ***4h.*** 133.8 mg, 60% yield, yellow solid, mp 143–145 ˚C; ^{1}H NMR (400 MHz, d_6-DMSO): δ (ppm) 9.35 (s, 1H), 8.25 (s, 1H), 8.11 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.50 (t, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO): δ (ppm) 152.6, 142.7, 137.9, 131.7, 130.4, 122.4, 121.8, 118.3; HRMS (ESI, m/z): Calcd. for $C_8H_7BrN_3$ $[M+H]^+$ 223.9818; found 223.9816.

1-(2-Bromophenyl)-1H-1,2,4-triazole ***4i***.[3b] 81.9 mg, 37% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.45 (s, 1H), 8.08 (s, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.31 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 152.3, 144.5, 136.5, 134.0, 130.9, 128.6, 128.2, 118.8.

1-(o-Tolyl)-1H-1,2,4-triazole ***4j***.[3b] 86.4 mg, 54% yield, brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.26 (s, 1H), 8.10 (s, 1H), 7.41 – 7.27 (m, 4H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 152.2, 144.0, 136.3, 134.0, 131.7, 129.8, 127.0, 126.2, 18.0.

*1-(3,5-Dimethylphenyl)-1H-1,2,4-triazole 4****k.*** 111.3 mg, 64% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.48 (s, 1H), 8.02 (s, 1H), 7.24 (d, J = 14.7 Hz, 2H), 6.95 (s, 1H), 2.31 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 152.4, 140.9, 139.7, 136.9, 129.8, 117.8, 21.3; HRMS (ESI, m/z): Calcd. for $C_{10}H_{12}N_3$ $[M+H]^+$ 174.1026; found 174.1025.

1-(3-Chloro-4-methylphenyl)-1H-1,2,4-triazole ***4l***.[3b] 126.9 mg, 66% yield, brown solid, mp 123–125 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.52 (s, 1H), 8.07 (s, 1H), 7.69 (s, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 152.8, 141.0, 136.4, 135.8, 135.6, 132.0, 120.9, 118.1, 19.9.

ASSOCIATED CONTENT

Supporting Information

Copies of the ^{1}H NMR and ^{13}C NMR spectra for all compounds are available in the supporting Information

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Notes

The authors declare no competing financial interest.

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