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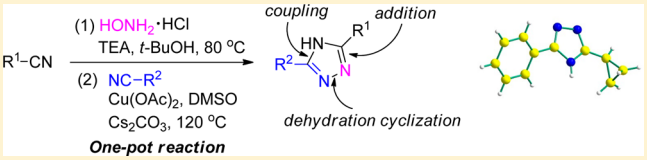
Copper-Catalyzed One-Pot Synthesis of 1,2,4-Triazoles from Nitriles and Hydroxylamine

Hao Xu,* Shuang Ma, Yuanqing Xu,* Longxiang Bian, Tao Ding, Xiaomin Fang, Wenkai Zhang, and Yanrong Ren

Institute of Fine Chemistry and Engineering, Henan Engineering Laboratory of Flame-Retardant and Functional Materials, College of Chemistry and Chemical Engineering, Henan University, Kaifeng 475004, P. R. China

Supporting Information

ABSTRACT: A simple and efficient copper-catalyzed one-pot synthesis of substituted 1,2,4-triazoles through reactions of two nitriles with hydroxylamine has been developed. The protocol uses simple and readily available nitriles and hydroxylamine hydrochloride as the starting materials and inexpensive $Cu(OAc)_2$ as the catalyst, and the corresponding 1,2,4-triazole derivatives are obtained in moderate to good yields. The reactions include sequential intermolecular addition of hydroxylamine to one nitrile to provide amidoxime, copper-catalyzed treatment of the amidoxime with another nitrile, and intramolecular dehydration/cyclization. This finding provides a new and useful strategy for synthesis of 1,2,4-triazole derivatives.



INTRODUCTION

Substituted 1,2,4-triazoles and their derivatives are key skeletons of many biologically active molecules and important organic compounds, and they exhibit wide applications in pesticides, medicines, functional materials, and organocatalysts.[1,2] In addition, a number of natural products contain a 1,2,4-triazole motif.[3] Because of their important properties and applications, various methods for the synthesis of 1,2,4-triazole derivatives have been developed.[4] In the previous methods, intramolecular cyclization of *N*-acyl amidrazones obtained from hydrazines and carboxylic acid derivatives is a common strategy.[5] However, the method often involves tedious synthetic procedures and low yields. Therefore, the development of a simple and practical procedure to access 1,2,4-triazole derivatives is still highly desirable. Currently, the transition-metal-catalyzed formation of N-heterocycles continues to be an active field,[6] but the transition-metal-catalyzed synthesis of 1,2,4-triazoles from readily available starting materials is relatively rare.[7] Furthermore, there remain some limitations such as inconvenient starting materials, harsh reaction conditions, and low yields in the reported transition-metal-catalyzed procedures. In 2009, Nagasawa's group developed a simple and efficient copper-catalyzed synthesis of 1,2,4-triazole derivatives via coupling of amidines with nitriles,[7a] which was the first example of the transition-metal-catalyzed synthesis of 1,2,4-triazole derivatives using readily available starting materials. Subsequently, we reported a convenient and efficient copper-catalyzed one-pot synthesis of 1,2,4-triazoles via sequential coupling and aerobic oxidative dehydrogenation of amidines.[7b] Very recently, Beifuss's group developed a novel and efficient copper-catalyzed cascade reaction between imidates and ammonium carbonate for the synthesis of symmetrically substituted 3,5-diaryl-1,2,4-triazoles.[7d] The methods above are efficient, but most of them use amidines or imidates as the substrates, which are usually prepared from nitriles.[8] In an attempt to use simple nitriles as the substrates in order to improve the previous procedures, Ma and co-workers reported a simple copper-mediated, one-pot three-component synthesis of symmetrically substituted 1,2,4-triazoles from amines and aryl nitriles under microwave assistance.[7f] Unfortunately, the reaction needs 2 equiv of Cu salt, and the yields of cyclization products are 12−55%. This prompted us to study the feasibility of synthesizing 1,2,4-triazoles from nitriles or other simple substrates under copper catalysis. On the basis of the coordination ability of transition metals to activate nitriles[9] and the great achievements in copper-catalyzed couplings and synthesis of N-heterocycles,[10] herein we report a simple and efficient copper-catalyzed one-pot synthesis of symmetrically and unsymmetrically substituted 1,2,4-triazoles from nitriles and hydroxylamine.

RESULTS AND DISCUSSION

At first, sequential reactions of cyclopropanecarbonitrile (**1h**) with hydroxylamine hydrochloride and 4-methylbenzonitrile (**1b**) were chosen as the model to optimize the conditions, including the catalyst, base, and solvent. As shown in Table 1, the one-pot synthesis of 3-cyclopropyl-5-(*p*-tolyl)-4*H*-1,2,4-triazole (**2j**) proceeded by a sequential two-step procedure. The first step, nucleophilic addition of hydroxylamine to **1h**, was performed in the presence of triethylamine (TEA) at 80 °C for 18 h without exclusion of air to provide *N*-hydroxycyclopropanecarboxamidine (**A**). The second step, a copper-catalyzed cascade reaction including intermolecular coupling of **A** with **1b** and intramolecular dehydration/cyclization, was carried out at 120 °C for 24 h. Nine copper catalysts (0.2 equiv) were tested

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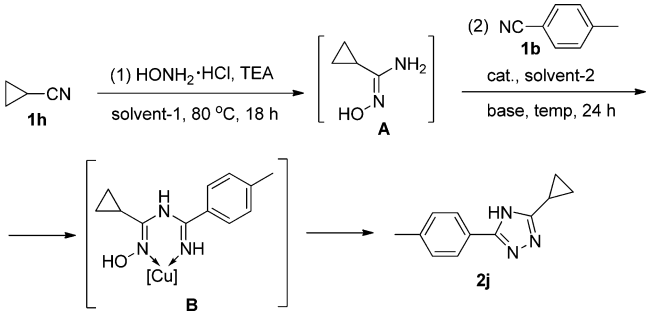
Table 1. Copper-Catalyzed One-Pot Synthesis of 3-Cyclopropyl-5-(*p*-tolyl)-4*H*-1,2,4-triazole (2j) via Sequential Reaction of Cyclopropanecarbonitrile (1h) with Hydroxylamine and 4-Methylbenzonitrile (1b): Optimization of Conditions[a]



entry	Cu cat.	base	solvent-1/solvent-2	T (°C)	yield of **2j** (%)[b]
1	CuI	Cs_2CO_3	*t*-BuOH/DMSO	120	27
2	CuBr	Cs_2CO_3	*t*-BuOH/DMSO	120	25
3	CuCl	Cs_2CO_3	*t*-BuOH/DMSO	120	16
4	Cu_2O	Cs_2CO_3	*t*-BuOH/DMSO	120	19
5	CuO	Cs_2CO_3	*t*-BuOH/DMSO	120	53
6	$CuCl_2$	Cs_2CO_3	*t*-BuOH/DMSO	120	5
7	$CuSO_4$	Cs_2CO_3	*t*-BuOH/DMSO	120	5
8	$Cu(OAc)_2$	Cs_2CO_3	*t*-BuOH/DMSO	120	60
9	Cu	Cs_2CO_3	*t*-BuOH/DMSO	120	35
10[c]	PTSA	–	*t*-BuOH/DMSO	120	0
11	–	Cs_2CO_3	*t*-BuOH/DMSO	120	0
12	$Cu(OAc)_2$	Cs_2CO_3	EtOH/DMSO	120	52
13	$Cu(OAc)_2$	Cs_2CO_3	CH_3OH/DMSO	120	5
14	$Cu(OAc)_2$	Cs_2CO_3	THF/DMSO	120	6
15	$Cu(OAc)_2$	Cs_2CO_3	*i*-PrOH/DMSO	120	5
16	$Cu(OAc)_2$	Cs_2CO_3	*t*-BuOH/DMF	120	44
17	$Cu(OAc)_2$	Cs_2CO_3	*t*-BuOH/Xylene	120	48
18	$Cu(OAc)_2$	Cs_2CO_3	*t*-BuOH/DCB	120	46
19	$Cu(OAc)_2$	K_2CO_3	*t*-BuOH/DMSO	120	57
20	$Cu(OAc)_2$	Na_2CO_3	*t*-BuOH/DMSO	120	13
21	$Cu(OAc)_2$	K_3PO_4	*t*-BuOH/DMSO	120	23
22	$Cu(OAc)_2$	Cs_2CO_3	*t*-BuOH/DMSO	100	19
23	$Cu(OAc)_2$	Cs_2CO_3	*t*-BuOH/DMSO	140	45
24[d]	$Cu(OAc)_2$	Cs_2CO_3	*t*-BuOH/DMSO	120	45
25[e]	$Cu(OAc)_2$	Cs_2CO_3	*t*-BuOH/DMSO	120	60

[a]Reaction conditions: Air was not excluded. For the first step, **1h** (0.45 mmol), hydroxylamine hydrochloride (0.5 mmol), TEA (0.9 mmol), anhydrous solvent-1 (1.5 mL), 80 °C, 18 h. For the second step, **1b** (0.3 mmol), catalyst (0.06 mmol), base (0.9 mmol), anhydrous solvent-2 (1.0 mL), anhydrous sodium sulfate (2.1 mmol), temperature, 24 h in a sealed Schlenk tube. [b]Isolated yields. [c]Using 20 mol % PTSA as catalyst without addition of base. [d]Under O_2 for the two steps. [e]Under N_2 for the two steps.

using anhydrous *t*-BuOH as the solvent in the first step, 3 equiv (relative to the amount of **1b**) of Cs_2CO_3 as the base, and anhydrous DMSO as the solvent in the second step (entries 1–9), and $Cu(OAc)_2$ showed the highest activity (entry 8). No target product (**2j**) was observed in the absence of copper catalyst or using 20 mol % *p*-toluenesulfonic acid (PTSA) as the catalyst without the addition of base (entries 10 and 11). We attempted to use various anhydrous solvents (entries 8 and 12–18), and *t*-BuOH as the solvent in the first step and DMSO as the solvent in the second step were the best choice (entry 8). The effect of the base in the second step was also investigated (entries 8 and 19–21), and Cs_2CO_3 provided the highest yield. We tried different temperatures (entries 8, 22, and 23), and 120 °C was suitable. The yield decreased because of hydrolysis of an extra amount of **1b** when the temperature was raised to 140 °C (entry 23). The second step was performed under O_2 (entry 24), and a low yield was obtained. Performing the second step under N_2 (entry 25) provided a 60% yield. The result proved that the second-step reaction could furnish the desired product without the requirement of O_2. In addition, the reaction did not need additional ligands or additives, implying that the substrates **1h** and **1b** could act as ligands, in accordance with reports of nitriles as ligands in previous research.[11]

The scope of the copper-catalyzed one-pot synthesis of 1,2,4-triazole derivatives was investigated under the optimized conditions. As shown in Table 2, most of the substrates examined provided moderate to good yields. Delightfully, homogeneous reactions of aromatic nitriles were performed well (entries 1–6), and various electron-donating groups (EDGs) (Me, OMe; entries 2 and 5) and electron-withdrawing groups (EWGs) (Cl, NO_2; entries 3 and 4) in the substituents as well as an N-heterocyclic nitrile (entry 6) were completely tolerated in this transformation. Reactions between aromatic nitriles and aliphatic nitriles gave heterogeneous products in moderate yields (entries 7–19). Generally, steric hindrance by the substrates could lower the yield (entries 12, 14, 15, and 18). Furthermore, the position of the substituents on the aryl group (*para* vs *meta* position) affected the yield of **2**, with the *para*-substituted substrates giving relatively higher yields (compare entries 10 and 19). In the copper-catalyzed one-pot couplings, no ligand or additive was required. The method could tolerate various functional groups in the substrates, including ether (entry 5), a C–Cl bond (entries 3 and 11–15), nitro (entries 4 and 16–18), and N-heterocycle (entry 6).

Interestingly, under acidic conditions, the reaction of amidoximes with nitriles can afford 1,2,4-oxadiazoles when PTSA/$ZnCl_2$ is used as the catalyst, as reported by Augustine and co-workers in 2009.[12] However, under basic conditions, 1,2,4-triazoles were synthesized from nitriles and amidoximes (obtained by the reaction of nitriles with hydroxylamine) in our work. The structure of compound **2h** was confirmed by X-ray crystallography (Figure S1 in Supporting Information).

A possible mechanism is proposed for synthesis of 1,2,4-triazoles as shown in Scheme 1). At first, intermolecular nucleophilic addition of the amino group of hydroxylamine to the cyano group of R^1-CN in the presence of TEA leads to amidoxime **I**,[13] and then coupling of **I** with the copper complex of R^1-CN (**II**) affords intermediate **III**.[7f,14] Finally, intramolecular dehydration/cyclization of **III** gives the desired target product **2**, releasing the Cu(II) catalyst.

CONCLUSION

We have developed a simple and efficient copper-catalyzed one-pot method for the synthesis of 1,2,4-triazole derivatives. The protocol uses simple and readily available nitriles and hydroxylamine hydrochloride as the starting materials and inexpensive $Cu(OAc)_2$ as the catalyst, and the catalytic cycle is achieved without the protection of an inert gas. The one-pot reactions include sequential intermolecular addition of hydroxylamine to one nitrile to afford an amidoxime, copper-catalyzed treatment of the amidoxime with another nitrile, and intramolecular dehydration/cyclization without the addition of ligand and additive, and the corresponding 1,2,4-triazole derivatives are obtained in moderate to good yields. The present

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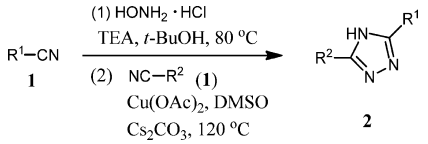
Table 2. Copper-Catalyzed One-Pot Synthesis of Substituted 1,2,4-Triazoles[a]



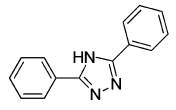
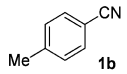
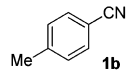
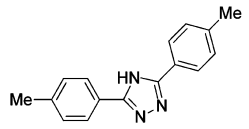
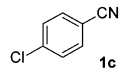
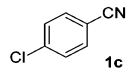
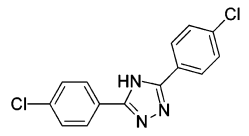
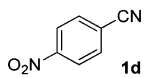
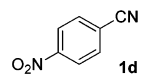
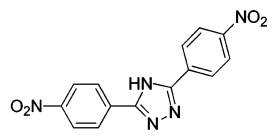
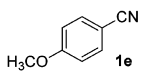
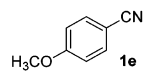
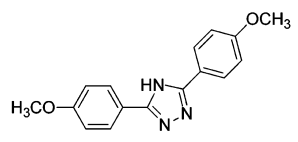
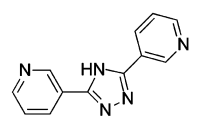
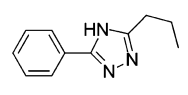
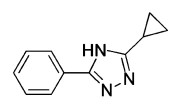
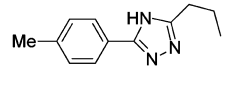
Entry	R^1-CN (1)	R^2-CN (1)	2	Yield (%)[b]
1	 1a	 1a	 2a	63
2	 1b	 1b	 2b	62
3	 1c	 1c	 2c	66
4	 1d	 1d	 2d	73
5	 1e	 1e	 2e	82
6	 1f	 1f	 2f	83
7	 1g	**1a**	 2g	52
8	 1h	**1a**	 2h	65
9	**1g**	**1b**	 2i	50

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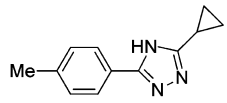
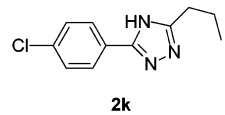
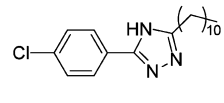
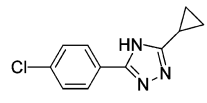
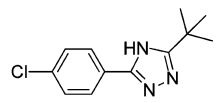
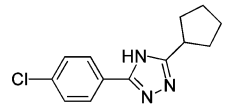
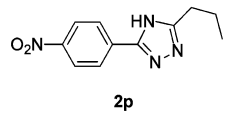
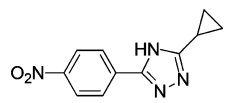
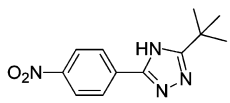
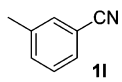
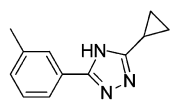
Table 2. continued

Entry	R^1-CN (**1**)	R^2-CN (**1**)	**2**	Yield (%)[b]
10	**1h**	**1b**	 **2j**	60
11	**1g**	**1c**	 **2k**	55
12	 **1i**	**1c**	 **2l**	43
13	**1h**	**1c**	 **2m**	68
14	 **1j**	**1c**	 **2n**	48
15	 **1k**	**1c**	 **2o**	45
16	**1g**	**1d**	 **2p**	51
17	**1h**	**1d**	 **2q**	55
18	**1j**	**1d**	 **2r**	46
19	**1h**	 **1l**	 **2s**	42

[a]Reaction conditions: Air was not excluded. For the first step, R^1-CN (**1**) (0.45 mmol), hydroxylamine hydrochloride (0.5 mmol), triethylamine (TEA) (0.9 mmol), anhydrous *t*-BuOH (1.5 mL), 80 °C, 18 h. For the second step, R^2-CN (**1**) (0.3 mmol), $Cu(OAc)_2$ (0.06 mmol), Cs_2CO_3 (0.9 mmol), anhydrous DMSO (1 mL), anhydrous sodium sulfate (2.1 mmol), 120 °C, 24 h in a sealed Schlenk tube. [b]Isolated yields.

method can tolerate various functional groups, including ether, a C−Cl bond, nitro, and N-heterocycle, and shows economical and practical advantages over the previous methods, so it provides the opportunity for the construction of diverse and useful molecules. In view of the easy availability of the starting materials and the potential of the products,[1,2] the method will have a promising application in the synthesis for the 1,2,4-triazole drugs or organocatalysts.

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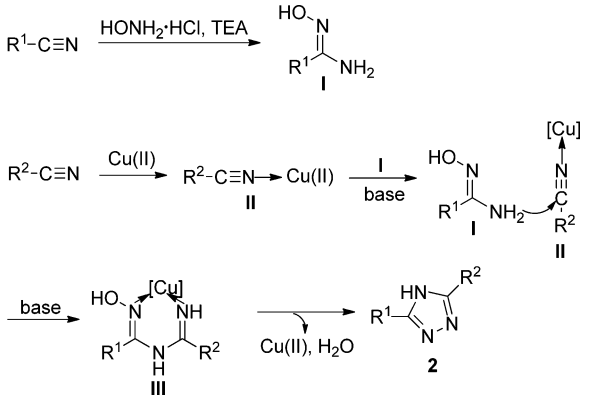
Scheme 1. Possible Mechanism for the Synthesis of 1,2,4-Triazoles



EXPERIMENTAL SECTION

General Experimental Procedures. All of the reactions were carried out under air. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard (^{1}H NMR: TMS at 0.00 ppm, DMSO at 2.50 ppm; ^{13}C NMR: DMSO at 39.52 ppm).

General Procedure for the Synthesis of 1,2,4-Triazoles (2a−s). The first nitrile **1** (0.45 mmol), hydroxylamine hydrochloride (0.5 mmol, 34.7 mg), triethylamine (0.9 mmol, 126 μL), and anhydrous *t*-BuOH (1.5 mL) were added to a 25 mL Schlenk tube charged with a magnetic stirrer. The reaction mixture was stirred at 80 °C for 18 h without exclusion of air for the first step. The second nitrile **1** (0.3 mmol), $Cu(OAc)_2$ (0.06 mmol, 12 mg), Cs_2CO_3 (0.9 mmol, 293 mg), anhydrous DMSO (1.0 mL), and anhydrous sodium sulfate (2.1 mmol, 0.3 g) were added to the Schlenk tube, and the mixture was stirred at 120 °C for another 24 h in the sealed Schlenk tube for the second step. The resulting solution was concentrated on a rotary evaporator, and the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as the eluent to give the desired target product **2a−s**.

3,5-Diphenyl-4*H*-1,2,4-triazole (2a).[7a] Eluent: petroleum ether/ethyl acetate (6:1). Yield 42 mg (63%). White solid, mp 190.2−191.0 °C (lit.[7a] mp 190−191 °C). ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 14.62 (s, 1H), 8.36−8.06 (s, 4H), 7.67−7.21 (m, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 162.2, 155.6, 131.9, 130.6, 129.5, 129.2, 127.8, 126.6. ESI-MS $[M + H]^+$ *m*/*z* 222.1.

3,5-Di-*p*-tolyl-4*H*-1,2,4-triazole (2b).[7b] Eluent: petroleum ether/ethyl acetate (6:1). Yield 46 mg (62%). White solid, mp 259.5−259.6 °C (lit.[7b] mp 249−251 °C). ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 14.37 (s, 1H), 8.04−7.91 (m, 4H), 7.46−7.21 (m, 4H), 2.44−2.30 (m, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 162.0, 155.4, 140.4, 138.8, 130.1, 129.7, 129.1, 126.5, 126.3, 125.0, 21.4. ESI-MS $[M + H]^+$ *m*/*z* 250.1.

3,5-Bis(4-chlorophenyl)-4*H*-1,2,4-triazole (2c).[7b] Eluent: petroleum ether/ethyl acetate (6:1). Yield 57 mg (66%). White solid, mp 288.4−288.8 °C (lit.[7b] mp 292−294 °C). ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 14.69 (s, 1H), 8.21−7.95 (m, 4H), 7.71−7.46 (m, 4H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 161.2, 154.8, 135.0, 134.8, 130.2, 129.9, 129.4, 128.8, 128.2, 126.6. ESI-MS $[M + H]^+$ *m*/*z* 290.0.

3,5-Bis(4-nitrophenyl)-4*H*-1,2,4-triazole (2d).[7c] Eluent: petroleum ether/ethyl acetate (6:1). Yield 68 mg (73%). Yellow solid, mp 250.0−252.0 °C (lit.[7c] mp 246−248 °C). ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 14.56 (s, 1H), 8.46−8.13 (m, 8H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 157.5, 148.4, 135.1, 127.6, 124.7. ESI-MS $[M + H]^+$ *m*/*z* 312.5.

3,5-Bis(4-methoxyphenyl)-4*H*-1,2,4-triazole (2e).[15] Eluent: petroleum ether/ethyl acetate (6:1). Yield 69 mg (82%). White solid, mp 193−195 °C (lit.[15] mp 196−197 °C). ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 14.16 (s, 1H), 7.98 (d, *J* = 8.7 Hz, 4H), 7.17−6.93 (m, 4H), 3.79 (s, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 161.8, 161.1, 160.3, 155.2, 134.7, 128.2, 127.8, 124.6, 120.4, 116.9, 114.9, 114.5, 55.8, 55.6. ESI-MS $[M + H]^+$ *m*/*z* 282.3, $[M + Na]^+$ *m*/*z* 304.2.

3,5-Bis(pyridin-3-yl)-4*H*-1,2,4-triazole (2f).[16] Eluent: ethyl acetate. Yield 56 mg (83%). White solid, mp 230.0−233.2 °C (lit.[16] mp 231−232 °C). ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 14.96 (s, 1H), 9.30 (s, 2H), 8.83−8.58 (m, 2H), 8.49−8.40 (m, 2H), 7.61 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 174.4, 167.0, 160.0, 153.7, 152.3, 150.9, 149.1, 147.5, 135.6, 133.9, 127.2, 124.5. ESI-MS $[M + H]^+$ *m*/*z* 224.2, $[M + Na]^+$ *m*/*z* 246.2.

3-Phenyl-5-propyl-4*H*-1,2,4-triazole (2g).[17] Eluent: petroleum ether/ethyl acetate (6:1). Yield 29 mg (52%). White solid, mp 75.1−78.3 °C (lit.[17] mp 71−72 °C). ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 13.71 (s, 1H), 8.03 (d, *J* = 7.1 Hz, 2H), 7.59−7.29 (m, 3H), 2.73 (t, *J* = 6.9 Hz, 2H), 1.83−1.68 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 161.2, 157.7, 132.2, 129.0, 126.2, 40.6, 28.2, 21.3, 14.0. ESI-MS $[M + H]^+$ *m*/*z* 188.1.

3-Cyclopropyl-5-phenyl-4*H*-1,2,4-triazole (2h).[7b] Eluent: petroleum ether/ethyl acetate (6:1). Yield 36 mg (65%). White solid, mp 201.4−201.5 °C (lit.[7b] mp 202−204 °C). ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 14.11−13.58 (m, 1H), 7.95 (d, *J* = 7.2 Hz, 2H), 7.66−7.28 (m, 3H), 2.19−1.89 (s, 1H), 1.26−0.68 (m, 4H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 161.3, 159.8, 132.4, 130.2, 129.1, 126.2, 8.5, 7.6. ESI-MS $[M + H]^+$ *m*/*z* 186.1.

3-Propyl-5-(*p*-tolyl)-4*H*-1,2,4-triazole (2i).[7b] Eluent: petroleum ether/ethyl acetate (6:1). Yield 30 mg (50%). White solid, mp 112.4−114.2 °C (lit.[7b] mp 140−142 °C). ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 14.01−13.57 (m, 1H), 7.92−7.79 (m, 2H), 7.37−7.17 (m, 2H), 2.75−2.57 (m, 2H), 2.33 (s, 3H), 1.78−1.65 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 161.3, 157.6, 138.4, 129.6, 129.5, 126.1, 28.2, 21.4, 21.3, 14.0. ESI-MS $[M + H]^+$ *m*/*z* 202.1.

3-Cyclopropyl-5-(*p*-tolyl)-4*H*-1,2,4-triazole (2j).[7b] Eluent: petroleum ether/ethyl acetate (6:1). Yield 36 mg (60%). White solid, mp 188.6−191.5 °C (lit.[7b] mp 186−188 °C). ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 14.21−13.21 (m, 1H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.39−7.07 (m, 2H), 2.33 (s, 3H), 2.12−1.93 (m, 1H), 1.12−0.74 (m, 4H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 161.2, 159.7, 138.5, 129.7, 126.2, 21.4, 8.5, 7.6. ESI-MS $[M + H]^+$ *m*/*z* 200.1.

3-(4-Chlorophenyl)-5-propyl-4*H*-1,2,4-triazole (2k). Eluent: petroleum ether/ethyl acetate (6:1). Yield 37 mg (55%). White solid, mp 123.0−124.1 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 14.20−13.68 (m, 1H), 8.04−7.87 (m, 2H), 7.65−7.40 (m, 2H), 2.79−2.57 (m, 2H), 1.81−1.64 (m, 2H), 1.02−0.78 (m, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 160.3, 158.4, 133.7, 131.1, 129.2, 127.8, 28.7, 21.2, 14.0. HRMS $[M + H]^+$ *m*/*z* calcd for $C_{11}H_{13}ClN_3$ 222.0798, found 222.0799.

3-(4-Chlorophenyl)-5-undecyl-4*H*-1,2,4-triazole (2l). Eluent: petroleum ether/ethyl acetate (6:1). Yield 43 mg (43%). White solid, mp 98.6−99.4 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 13.75 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 2.80−2.62 (m, 2H), 1.78−1.57 (m, 2H), 1.37−1.08 (m, 16H), 0.82 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 160.3, 158.0, 133.6, 131.1, 129.0, 127.8, 31.8, 29.5, 29.4, 29.3, 29.2, 29.0, 27.8, 26.2, 22.6, 14.3. HRMS $[M + H]^+$ *m*/*z* calcd for $C_{19}H_{29}ClN_3$ 334.2050, found 334.2056.

3-(4-Chlorophenyl)-5-cyclopropyl-4*H*-1,2,4-triazole (2m).[7b] Eluent: petroleum ether/ethyl acetate (6:1). Yield 45 mg (68%). White solid, mp 200.5−200.6 °C (lit.[7b] mp 202−203 °C). ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 14.23−13.55 (m, 1H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.58−7.41 (m, 2H), 2.14−2.00 (m, 1H), 1.14−0.86 (m, 4H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 160.1, 160.0, 133.7, 130.9, 129.1, 127.9, 8.6, 7.5. ESI-MS $[M + H]^+$ *m*/*z* 220.1.

3-(*tert*-Butyl)-5-(4-chlorophenyl)-4*H*-1,2,4-triazole (2n).[7b] Eluent: petroleum ether/ethyl acetate (8:1). Yield 34 mg (48%). White solid, mp 191.6−192.5 °C (lit.[7b] mp 165−167 °C). ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 14.17−13.60 (m, 1H), 8.02 (d, *J* = 8.5 Hz, 2H), 7.62−7.35 (m, 2H), 1.36 (s, 9H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 165.6, 159.8, 133.7, 131.1, 129.1, 127.9, 32.2, 29.5. ESI-MS $[M + H]^+$ *m*/*z* 236.1.

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3-(4-Chlorophenyl)-5-cyclopentyl-4*H*-1,2,4-triazole (2o). Eluent: petroleum ether/ethyl acetate (6:1). Yield 33 mg (45%). White solid, mp 187.2−189.4 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 14.16−13.62 (m, 1H), 8.13−7.91 (m, 2H), 7.64−7.39 (m, 2H), 3.29−3.05 (m, 1H), 2.12−1.91 (m, 2H), 1.89−1.53 (m, 6H). ^{13}C NMR (DMSO-d_6, 400 MHz, 25 °C) δ 161.8, 160.1, 133.7, 131.0, 129.1, 127.9, 37.0, 32.2, 25.5. HRMS [M + H]$^+$ m/z calcd for $C_{13}H_{15}ClN_3$ 248.0955, found 248.0953.

3-(4-Nitrophenyl)-5-propyl-4*H*-1,2,4-triazole (2p). Eluent: petroleum ether/ethyl acetate (6:1). Yield 36 mg (51%). Light-yellow solid, mp 148.5−149.0 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 14.53−13.74 (m, 1H), 8.22 (d, J = 8.8 Hz, 2H), 8.16 (d, J = 8.9 Hz, 2H), 2.71 (t, J = 7.5 Hz, 2H), 1.79−1.64 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 159.6, 158.5, 147.7, 138.1, 127.0, 124.4, 28.1, 21.2, 13.9. HRMS [M + H]$^+$ m/z calcd for $C_{11}H_{13}N_4O_2$ 233.1039, found 233.1036.

3-Cyclopropyl-5-(4-nitrophenyl)-4*H*-1,2,4-triazole (2q). Eluent: petroleum ether/ethyl acetate (6:1). Yield 38 mg (55%). Light-yellow solid, mp 218.3−221.1 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 14.05 (s, 1H), 8.27 (d, J = 9.0 Hz, 2H), 8.16 (d, J = 9.0 Hz, 2H), 2.16−2.04 (m, 1H), 1.11−0.92 (m, 4H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 161.1, 158.8, 147.8, 137.7, 127.1, 127.0, 124.4, 124.3, 8.7, 8.6, 7.6, 7.5. HRMS [M + H]$^+$ m/z calcd for $C_{11}H_{11}N_4O_2$ 231.0882, found 231.0881.

3-(*tert*-Butyl)-5-(4-nitrophenyl)-4*H*-1,2,4-triazole (2r). Eluent: petroleum ether/ethyl acetate (6:1). Yield 34 mg (46%). Yellow solid, mp 158.7−159.4 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 13.98 (s, 1H), 8.27 (d, J = 8.7 Hz, 2H), 8.20 (d, J = 8.9 Hz, 2H), 1.41−1.33 (m, 9H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 166.2, 159.1, 147.7, 138.2, 127.1, 124.4, 32.3, 29.4. HRMS [M + H]$^+$ m/z calcd for $C_{12}H_{15}N_4O_2$ 247.1195, found 247.1192.

3-Cyclopropyl-5-(*m*-tolyl)-4*H*-1,2,4-triazole (2s). Eluent: petroleum ether/ethyl acetate (6:1). Yield 25 mg (42%). White solid, mp 151.5−152.6 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 14.25−13.08 (m, 1H), 7.87−7.64 (m, 2H), 7.45−7.05 (m, 2H), 2.35 (s, 3H), 2.16−1.94 (m, 1H), 1.13−0.78 (m, 4H). ^{13}C NMR (DMSO-d_6, 100 MHz, 25 °C) δ 165.7, 161.1, 159.7, 154.6, 138.7, 138.1, 132.0, 131.0, 129.7, 129.3, 128.9, 127.8, 126.9, 126.7, 123.5, 123.3, 21.5, 21.3, 9.3, 8.5, 7.9, 7.5. HRMS [M + H]$^+$ m/z calcd for $C_{12}H_{14}N_3$ 200.1188, found 200.1188.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra of the synthesized compounds, and crystallographic data for **2h** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: xuhao@henu.edu.cn.

*E-mail: xuyuanqing@henu.edu.cn.

Notes

The authors declare no competing financial interest.

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