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A two-step continuous flow synthesis of 1,4-disubstituted 1,2,3-triazoles under metal- and azide-free conditions

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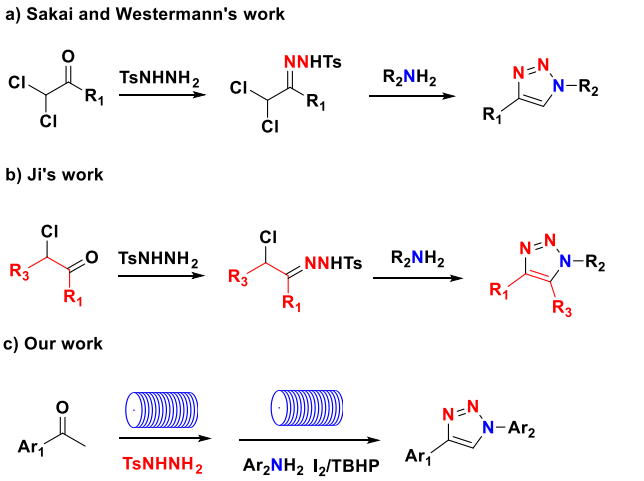
A green, general and efficient I_2/TBHP mediated synthetic method toward 1,4-disubstituted 1,2,3-triazoles via the reactions of acetophenones, tosylhydrazine and anilines within 35min in a two-step continuous flow system has been developed. The reaction proceeds smoothly to afford 1,4-disubstituted 1,2,3-triazoles in moderate to good yield under metal- and azide-free conditions by using I_2 as a catalyst.

Introduction

The formation of heterocyclic frameworks is an important part of programs in drug discovery. As an important compounds, 1,2,3-triazoles have been widely used in organic synthesis,[1] biochemistry,[2] and material science.[3] Therefore, it is important to develop general and efficient methods for their synthesis.[4] The pioneer work on the synthesis of 1,2,3-triazole can be dated back to the 1960s, Huisgen and co-workers reported the approach for the synthesis of these compounds through thermal dipolar cycloaddition between alkynes and azides.[5] However, the regioselectivity of this method is poor, which limits its application. Afterward, Sharpless[6] and Meldal[7] reported a Cu-catalyzed azide–alkyne cycloaddition (CuAAC) method for the synthesis of 1,2,3-triazole, which was high efficiency and had excellent regioselectivity. And 1,2,3-triazoles can also be prepared by RuAAC,[8] IrAAC,[9] and Pd-catalyzed reactions of alkenyl bromides with azides.[10] However, these reactions mentioned above shared a common drawback, which was that they utilized heavy metals, which limited its practical application.

To overcome this problem, another method was developed by using organic catalyst instead of metal catalyst.[11] And a lot of 1,2,3-triazoles had been readily obtained through the incorporation of azides with different reaction partners. For example the reaction of azides with enols and enamines, [12] the nitromethylene-based three-component synthesis[13] and the Lewis based-catalyzed azide-zwitterion reaction.[14] However, these reactions required sodium azides or organic azides, which were explosive and toxic. Therefore, it is important to develop an efficient and straightforward method to synthesis 1,2,3-triazoles from simple, readily accessible, and inexpensive materials.



Scheme 1 A proposed route to 1,2,3-triazoles under metal- and azide-free conditions

With the striking advances of 1,2,3-triazole synthesis, the most challenge is to develop a metal- and azide-free method, which is quite attractive from the economical and green chemistry points of view. In 2013, Zhang and coworkers provided a copper-mediated method to achieve the desired 1,4-disubstituted 1,2,3-triazoles without the use of azides.[15] Westermann improved Sakai's reaction and reported the synthesis of 1,4-disubstituted 1,2,3-triazoles under metal-free conditions (Scheme 1a).[16] Recently, Ramasastry summarized the synthetic methods for 1,2,3-triazoles.[17] To the best of our knowledge, only few literatures reported chemoselective formation of 1,4-disubstituted 1,2,3-triazoles under metal- and azide-free conditions. Ji and coworkers reported the synthesis of 1,4-disubstituted and 1,5-disubstituted 1,2,3-triazoles through the cycloaddition of α-chlorotosylhydrazones with arylamines under metal- and azide-free conditions (Scheme

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1b).[18] Wang and coworkers reported the I_2/TPBP mediated synthesis of 1,4-disubstituted 1,2,3-triazoles. [19] However, the starting materials of these methods were not readily available. They were always obtained through the reaction of ketones with tosylhydrazine, which added the step to get the desired products. And the added step in multistep batch reactions was not only troublesome, but also time-consuming and less efficient.

The use of continuous flow microreactors provides a valuable platform for the development of multistep syntheses. Because it integrates multiple unit operations into one single operation and eliminates the handling of intermediate species.[20] Recently, our group had researched the oxidation amination of alcohol to amide in a two-step continuous flow reactor with metal-free catalyst.[21] In the process, we successfully integrates alcohol oxidation and amide bond formation, which are usually accomplished separately, into a single operation. Here we report a I_2/TBHP metdiated two-step continuous flow synthesis of 1,4-disubstituted 1,2,3-triazoles (Scheme 1c).

Since the continuous flow system was fit for the multistep reaction, we designed a two-step continuous flow reactor system, as shown in Figure 1. It consists of three syringe pumps, two T-piece micromixers and two microreactors. The volume of the syringe and two microreactors are 20mL, 2mL and 10mL, respectively. The mole ratio of reactants and reaction time can be modulated by changing the flow rate of syringes. And the temperature was controlled by oil bath.

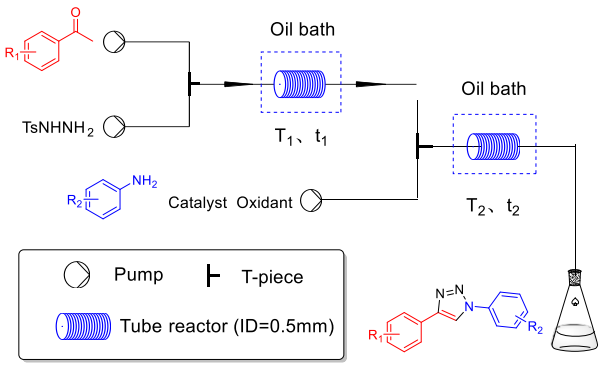
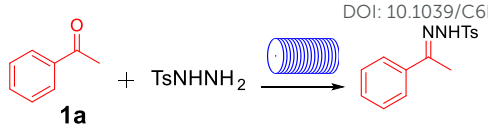


Figure 1 A two-step continuous flow reactor system

Results and Discussion

At the beginning, a model reaction of acetophenone (**1a**), tosylhydrazine and *p*-aminotoluene (**2a)** to form 4-phenyl-1-*p*-tolyl-1H-1,2,3-triazole (**3a**) were chosen to identify the reaction system. Firstly, we optimized the first step of the reaction in continuous flow reactor. The results were summarized in Table 1. Before we started the experiment in microreactor, a solvent screen in batch experiment was needed, which indicated that 1,4-dioxane was the optimal solvent due to the solubility of product. From Table 1 we can see that the reaction temperature and reaction time of the first step were 50°C (Table 1, entries 1-3) and 10min (Table 1, entry 2, 4, 5) , respectively.

Table 1 Optimization of the reaction conditions of the first step [a]

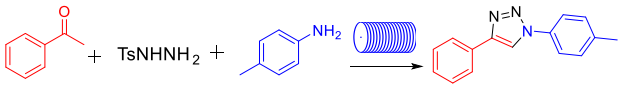


1a

Entry	Equiv. number	T_1 (°C)	t (min)	Yield (%) [b]
1	1:1	25	10	86
2	1:1	50	10	98
3	1:1	80	10	96
4[c]	1:1	50	5	95
5[d]	1:1	50	20	98
6[e]	1:1.2	50	10	96
7[f]	1.2:1	50	10	94

[a] Reaction conditions: solution A: 0.1M of **1a** in dioxane, flow rate 0.1mL/min; solution B: 0.1M of tosylhydrazine in dioxane, flow rate 0.1mL/min, unless otherwise noted. [b] Isolated yield. [c] solution A: 0.1M of **1a**, flow rate 0.2mL/min; solution B: 0.1M of tosylhydrazine in dioxane, flow rate 0.2mL/min. [d] solution A: 0.1M of **1a**, flow rate 0.05mL/min; solution B: 0.1M of tosylhydrazine in dioxane, flow rate 0.05mL/min. [e] solution A: 0.1M of **1a**, flow rate 0.1mL/min; solution B: 0.12M of tosylhydrazine in dioxane, flow rate 0.1mL/min. [f] solution A: 0.12M of **1a**, flow rate 0.1mL/min; solution B: 0.1M of tosylhydrazine in dioxane, flow rate 0.1mL/min.

Table 2 Optimization of the reaction conditions of the second step [a]



1a 2a 3a

Entry	Catalyst (mol%)	Oxidant (equiv.)	T_1 (°C)	T_2 (°C)	t_1 (min)	t_2 (min)	Yield (%) [b]
1	I_2 (10)	TBHP (2)	50	80	10	25	41
2	KI (10)	TBHP (2)	50	80	10	25	23
3	NIS (10)	TBHP (2)	50	80	10	25	38
4	I_2 (10)	H_2O_2 (2)	50	80	10	25	Trace
5	I_2 (10)	*m*-CPBA (2)	50	80	10	25	NP [c]
6	I_2 (10)	TEMPO (2)	50	80	10	25	NP
7	I_2 (10)	-	50	80	10	25	Trace
8	I_2 (10)	TBHP (2)	50	50	10	25	25
9	I_2 (10)	TBHP (2)	50	100	10	25	64
10[d]	I_2 (10)	TBHP (2)	50	100	10	16.7	48
11[e]	I_2 (10)	TBHP (2)	50	100	10	33.3	64
12[f]	I_2 (20)	TBHP (2)	50	100	10	25	85
13[g]	I_2 (50)	TBHP (2)	50	100	10	25	86

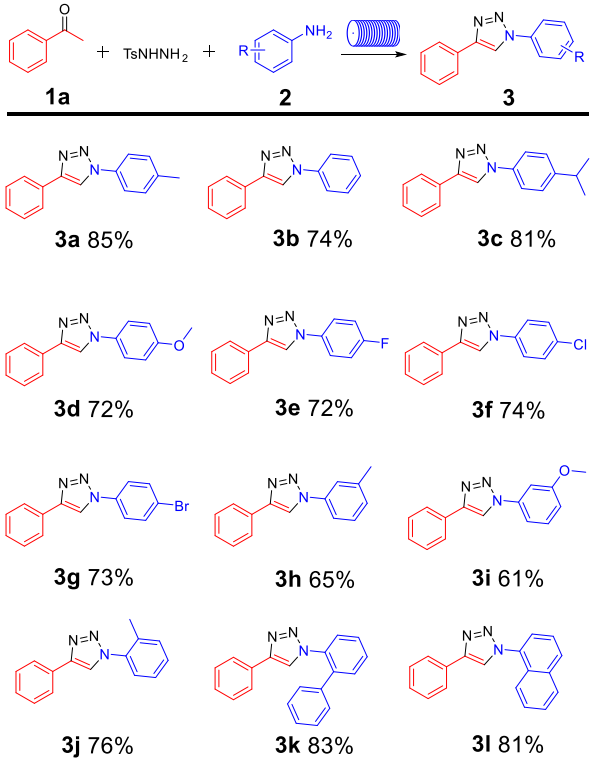
[a] Reaction conditions: solution A: 0.1M of **1a** in dioxane, flow rate 0.1mL/min; solution B: 0.1M of tosylhydrazine in dioxane, flow rate 0.1mL/min; solution C: 0.06M of **2a**, 0.005M of catalyst, 0.1M of oxidant in dioxane, flow rate 0.2mL/min, unless otherwise noted. [b] Isolated yield. [c] NP=No Product. [d] solution C: 0.03M of **2a**, 0.5mM of I_2, 0.05M of TBHP in dioxane, flow rate 0.4mL/min. [e] solution C: 0.12M of **2a**, 0.01M of I_2, 0.1M of TBHP in dioxane, flow rate 0.1mL/min. [f] solution C: 0.06M of **2a**, 0.01M of I_2, 0.1M of TBHP in dioxane, flow rate 0.2mL/min. [g] solution C: 0.06M of **2a**, 0.025M of I_2, 0.1M of TBHP in dioxane, flow rate 0.2mL/min.

Then we continued to optimize the second step which was initiated by treating acetophenone (**1a**), tosylhydrazine and *p*-aminotoluene (**2a)** with I_2 (10 mol %) in the presence of TBHP (2.0 equiv), 80 °C for 35min. The yield of the product **3a** was 41%. To improve the yield of the product, different catalysts,

oxidants, reaction temperature and reaction time were tested. And the results were shown in Table 2. The reaction proceeded less efficiently in other iodine-containing catalysts such as KI and NIS (Table 2, entries 1-3). And when other oxidants were used instead of TBHP, the results were really bad (Table 2, entries 1, 4-7). Next, the temperature was investigated and we observed that when increasing the temperature to 100°C, it led to a significant improvement in the amount of product **3a**. Thus, 100°C was regarded as the optimum temperature (Table 2, entry 1, 8, 9). The reaction time (Table 2, entry 1, 10, 11) and equiv. number of catalyst (Table 2, entry 1, 12, 13) were also investigated, which led to best reaction conditions.

Optimized reaction conditions for a two-step continuous flow synthesis of 1,2,3- triazole had been obtained. And we used the similar conditions to investigate the same reaction in batch. The yield of the product was only up to 43%, which was much lower than that in continuous flow system. And the reaction time in batch was 15 h, which was much longer than 35 min. Most importantly, the reaction in batch was much more troublesome. The two steps needed to be accomplished separately, *p*-aminotoluene, I_2 and TBHP in dioxane were added to the reaction liquid when acetophenone (**1a**) and tosylhydrazine were reacted completely and isolated, which led to time-consuming and less efficient. From these results we can see that the continuous flow system was fit for the multistep reaction.

Table 3 Scope of anilines [a]

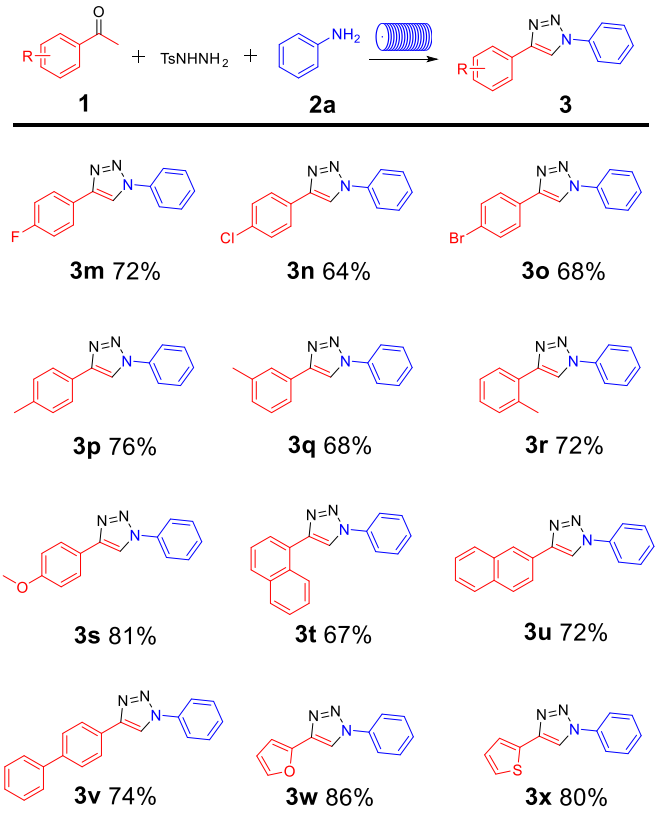


[a] Reaction conditions: solution A: 0.1M of **1a** in dioxane, flow rate 0.1mL/min; solution B: 0.1M of tosylhydrazine in dioxane, flow rate 0.1mL/min, T_1=50°C; solution C: 0.06M of **2**, 0.005M of I_2, 0.1M of TBHP in dioxane, flow rate 0.2mL/min, T_2=100°C.

With the optimized conditions in hand, an array of commercially available anilines was used to investigate the substrate scope of this method. And the results were shown in Table 3. Moderate to good yields were obtained in most cases. The reactions of aniline or 4-substituted anilines afforded corresponding product **3a**-**3d** in 72%-85% yields. And fluoro, chloro, and bromo group could be tolerated in the reaction conditions to generate the desired functionalized 1,4-disubstituted 1,2,3-triazoles in good yields (Table 3, **3e**–**3g**). What's more, the reaction was not affected by the position of the substituents on the aromatic ring of anilines (Table 3, **3h**-**3j**). When more sterically hindered substrate ([1,1'-biphenyl]-2-amine) was applied, the reaction proceeded smoothly (Table 3, **3k**).

Next, a wide range of acetophenones had also been used to test the substrate scope of the reaction, and the results were shown in Table 4. Both electron-deficient and electron-rich substrates could react smoothly to afford the desired products in good yields (Table 4, **3m**-**3s**). 1-acetonaphthone and 2-acetonaphthone were good substrates for this reaction (Table 4, **3t**, **3u**). Furthermore, triazoles with heterocyclic substituents, such as furyl and thiophenyl groups, were obtained in high yields (Table 4, **3w**, **3x**).

Table 4 Scope of acetophenones [a]



[a] Reaction conditions: solution A: 0.1M of **1** in dioxane, flow rate 0.1mL/min; solution B: 0.1M of tosylhydrazine in dioxane, flow rate 0.1mL/min, T_1=50°C; solution C: 0.06M of **2a**, 0.005M of I_2, 0.1M of TBHP in dioxane, flow rate 0.2mL/min, T_2=100°C.

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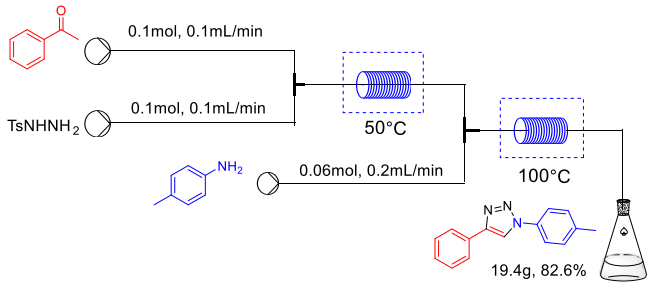

Scheme 2 A large-scale reaction in continuous flow system

To show the application of this new methodology, we conducted a large-scale reaction in continuous flow system under the best reaction conditions. And the desired product was obtained successfully in 83% yield (Scheme 2).

Conclusions

In conclusion, a green, efficient and direct method for the synthesis of 1,4- disubstituted 1,2,3-triazoles in a two-step continuous flow system has been developed. This metal- and azide-free method uses commercial available starting materials and integrates multistep reactions, which are usually accomplished separately, into a single operation. And the yield of the corresponding products was good. It also clearly shows the major advantage of continuous multistep systems to allow reaction parameters to be independently adjusted.

Experimental

General details

Reaction solvents were obtained commercially, and used without further purification. Commercial reagents were used as received. Reaction were monitored by thin-layer chromatography (TLC) on 0.25mm precoated Merck Silica Gel 60 F254, visualizing with ultraviolet light. $^1H/^{13}C$ NMR spectra were recorded on 400'54 ascend purchased from Bruker Biospin AG, operating at 400/100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as internal standard. High-resolution mass spectra (HRMS) were obtained from an Agilent 6520 LC-MS instrument. Flash column chromatography was performed on Merck Silica Gel 60 (200-300mesh) using petroleum ether and ethyl acetate.

General procedure for synthesis of compound 3: 5mmol of acetophenones (**1**) was dissolved in 50mL dioxane, which was placed into syringe A. And 5mmol of tosylhydrazine was dissolved in 50mL dioxane, which was placed into syringe B. Anilines (**2**, 3mmol, 1.2eq), I_2 (0.25mmol, 0.2eq) and TBHP (70wt% in water, 5mmol, 2eq) were dissolves in 50mL dioxane, which was placed into syringe C. The flow rate of syringes A, B and C were 0.1mL/min, 0.1mL/min, and 0.2mL/min, respectively. And the temperature of the two oil baths was set in 50˚C and 80˚C, respectively. The reaction liquid was collected, and then quenched by $NaHSO_3$ solution and extracted with ethyl acetate, washed with H_2O. The organic layer was dried over anhydrous sodium sulfate and solvent was removed under vacuum. And the crude product was purified by flash chromatography on silica gel by gradient elution with ethyl acetate in petroleum ether to obtain the product **3**.

4-phenyl-1-p-tolyl-1H-1,2,3-triazole (**3a**): White solid; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.92 (d, *J* = 7.2 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.36 (dd, *J* = 14.0, 7.8 Hz, 3H), 2.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.25, 137.90, 129.26, 128.43, 127.90, 127.35, 124.84, 119.46, 117.79, 116.59, 20.11; HRMS (ESI) m/z calcd for $C_{15}H_{13}N_3$ $[M+H]^+$ 236.1182, found 236.1195.

1,4-diphenyl-1H-1,2,3-triazole (**3b**): White solid; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.92 (d, *J* = 7.3 Hz, 2H), 7.81 (d, *J* = 7.7 Hz, 2H), 7.56 (t, *J* = 7.7 Hz, 2H), 7.47 (t, *J* = 6.5 Hz, 3H), 7.38 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.42, 136.09, 129.24, 128.79, 127.93, 127.78, 127.44, 124.87, 119.56, 116.61; HRMS (ESI) m/z calcd for $C_{14}H_{11}N_3$ $[M+H]^+$ 222.1047, found 222.1053.

1-(4-isopropylphenyl)-4-phenyl-1H-1,2,3-triazole (**3c**): White solid; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.94–7.88 (m, 2H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.38 (dd, *J* = 15.2, 7.9 Hz, 3H), 3.00 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.31 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.25, 130.29, 128.92, 128.39, 127.73, 125.87, 120.64, 117.66, 33.87, 23.91; HRMS (ESI) m/z calcd for $C_{17}H_{17}N_3$ $[M+H]^+$ 264.1495, found 264.1509.

1-(4-methoxyphenyl)-4-phenyl-1H-1,2,3-triazole (**3d**): Light yellow solid; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.93–7.88 (m, 2H), 7.71–7.65 (m, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.05 (d, *J* = 9.0 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.38, 128.92, 128.35, 125.85, 122.24, 117.86, 114.83, 55.66; HRMS (ESI) m/z calcd for $C_{15}H_{13}N_3O$ $[M+H]^+$ 252.1131, found 252.1146.

1-(4-fluorophenyl)-4-phenyl-1H-1,2,3-triazole (**3e**): White solid; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.91 (d, *J* = 7.9 Hz, 2H), 7.78 (dd, *J* = 8.8, 4.5 Hz, 2H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.24 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.56, 129.10, 127.95, 124.86, 121.57, 121.48, 116.72, 115.87, 115.64; HRMS (ESI) m/z calcd for $C_{14}H_{10}N_3F$ $[M+H]^+$ 240.0932, found 240.0958.

1-(4-chlorophenyl)-4-phenyl-1H-1,2,3-triazole (**3f**): Light yellow solid; ^1H NMR (400 MHz, DMSO) δ 7.97–7.93 (m, 4H), 7.66–7.60 (m, 2H), 7.54 –7.48 (m, 4H); ^{13}C NMR (101 MHz, DMSO) δ 167.82, 132.82, 130.75, 129.91, 129.22, 129.02, 128.53, 125.32, 121.65, 119.71; HRMS (ESI) m/z calcd for $C_{14}H_{10}N_3Cl$ $[M+H]^+$ 256.0636, found 256.0664.

1-(4-bromophenyl)-4-phenyl-1H-1,2,3-triazole (**3g**): White solid; ^1H NMR (400 MHz, DMSO) δ 9.36 (s, 1H), 7.99–7.90 (m, 4H), 7.90–7.82 (m, 2H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, DMSO) δ 145.20, 135.82, 132.84, 130.07, 129.02, 128.33, 125.33, 121.87, 119.65; HRMS (ESI) m/z calcd for $C_{14}H_{10}N_3Br$ $[M+H]^+$ 300.0131, found 300.0131.

4-phenyl-1-m-tolyl-1H-1,2,3-triazole (**3h**): White solid; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.95–7.89 (m, 2H), 7.64 (s, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.50–7.34 (m, 5H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.05, 130.32, 129.56, 128.92,

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128.40, 125.88, 121.24, 117.63, 21.45; HRMS (ESI) m/z calcd for $C_{15}H_{13}N_3$ $[M+H]^+$ 236.1182, found 236.1208.

1-(3-methoxyphenyl)-4-phenyl-1H-1,2,3-triazole (**3i**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.92 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.50–7.35 (m, 5H), 7.32 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.99 (dd, *J* = 8.3, 1.8 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.65, 147.36, 137.10, 129.54, 129.23, 127.91, 127.43, 124.87, 116.64, 113.63, 111.38, 105.38, 54.65; HRMS (ESI) m/z calcd for $C_{15}H_{13}N_3O$ $[M+H]^+$ 252.1131, found 252.1125.

4-phenyl-1-o-tolyl-1H-1,2,3-triazole (**3j**): light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.92 (d, *J* = 7.2 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 6.4 Hz, 1H), 7.35-7.42 (m, 3H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.6, 136.5, 133.7, 131.5, 130.3, 129.9, 128.9, 128.3, 126.8, 125.9, 125.8, 121.1, 17.9; HRMS (ESI) m/z calcd for $C_{15}H_{13}N_3$ $[M+H]^+$ 236.1182, found 236.1198.

1-(biphenyl-2-yl)-4-phenyl-1H-1,2,3-triazole (**3k**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.57 (m, 3H), 7.53–7.45 (m, 3H), 7.31 (dd, *J* = 9.4, 5.3 Hz, 3H), 7.25–7.20 (m, 4H), 7.10–7.06 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.40, 136.29, 135.95, 134.26, 130.13, 129.30, 128.87, 127.76, 127.74, 127.60, 127.50, 127.15, 127.04, 125.50, 124.74, 120.68; HRMS (ESI) m/z calcd for $C_{20}H_{15}N_3O$ $[M+H]^+$ 298.1339, found 298.1377.

1-(naphthalen-1-yl)-4-phenyl-1H-1,2,3-triazole (**3l**): Brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18–8.10 (m, 2H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.98 (dd, *J* = 6.7, 5.2 Hz, 2H), 7.73–7.53 (m, 4H), 7.49 (dd, *J* = 7.8, 4.2 Hz, 3H), 7.40 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.77, 134.23, 133.76, 130.48, 130.21, 129.00, 128.48, 128.40, 128.33, 127.96, 127.13, 125.93, 125.04, 123.60, 122.33; HRMS (ESI) m/z calcd for $C_{18}H_{13}N_3O$ $[M+H]^+$ 272.1182, found 272.1196.

4-(4-fluorophenyl)-1-phenyl-1H-1,2,3-triazole (**3m**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.89 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.56 (t, *J* = 7.7 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.16 (t, *J* = 8.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.05, 160.59, 146.54, 135.98, 128.81, 127.86, 126.64, 126.56, 125.44, 125.40, 119.53, 116.38, 115.05, 114.83; HRMS (ESI) m/z calcd for $C_{14}H_{10}N_3F$ $[M+H]^+$ 240.0892, found 240.0896.

4-(4-chlorophenyl)-1-phenyl-1H-1,2,3-triazole (**3n**): White solid; ^{1}H NMR (400 MHz, DMSO) δ 9.38 (s, 1H), 7.97 (t, *J* = 8.4 Hz, 4H), 7.69–7.50 (m, 5H); ^{13}C NMR (101 MHz, DMSO) δ 146.20, 136.53, 132.67, 130.20, 129.96, 129.14, 129.09, 128.82, 126.99, 120.02; HRMS (ESI) m/z calcd for $C_{14}H_{10}N_3Cl$ $[M+H]^+$ 256.0563, found 256.0576.

4-(4-bromophenyl)-1-phenyl-1H-1,2,3-triazole (**3o**): White solid; ^{1}H NMR (400 MHz, DMSO) δ 9.39 (s, 1H), 7.94 (dd, *J* = 16.4, 8.0 Hz, 4H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.65 (t, *J* = 7.9 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, DMSO) δ 146.27, 136.57, 131.99, 129.96, 129.48, 128.83, 127.27, 121.25, 120.02; HRMS (ESI) m/z calcd for $C_{14}H_{10}N_3Br$ $[M+H]^+$ 300.0038, found 300.0064.

1-phenyl-4-p-tolyl-1H-1,2,3-triazole (**3p**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.86–7.75 (m, 4H), 7.56 (dd, *J* = 10.5, 5.0 Hz, 2H), 7.46 (dd, *J* = 10.6, 4.3 Hz, 1H), 7.30–7.26 (m, 2H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.46, 137.32, 136.09, 128.75, 128.59, 127.69, 126.37, 124.73, 119.50, 116.21, 20.32; HRMS (ESI) m/z calcd for $C_{15}H_{13}N_3$ $[M+H]^+$ 236.1143, found 236.1175.

1-phenyl-4-m-tolyl-1H-1,2,3-triazole (**3q**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.83–7.76 (m, 3H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 2H), 7.50–7.44 (m, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.63, 134.56, 132.62, 128.77, 128.22, 127.81, 127.76, 125.53, 121.93, 119.52, 116.56, 20.46; HRMS (ESI) m/z calcd for $C_{15}H_{13}N_3$ $[M+H]^+$ 236.1143, found 236.1164.

1-phenyl-4-o-tolyl-1H-1,2,3-triazole (**3r**): light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.80-7.85 (m, 3H), 7.56 (t, *J* = 7.6 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.31 (d, *J* = 2.8 Hz, 3H), 2.55 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.81, 137.03, 135.72, 130.91, 129.84, 129.52, 129.03, 128.72, 128.42, 126.13, 120.51, 119.72, 21.43; HRMS (ESI) m/z calcd for $C_{15}H_{13}N_3$ $[M+H]^+$ 236.1143, found 236.1154.

4-(4-methoxyphenyl)-1-phenyl-1H-1,2,3-triazole (**3s**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.85 (d, *J* = 8.7 Hz, 2H), 7.79 (d, *J* = 7.9 Hz, 2H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.00 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.78, 147.25, 134.95, 128.75, 127.67, 126.16, 121.88, 119.48 , 115.76, 113.31, 54.34; HRMS (ESI) m/z calcd for $C_{15}H_{13}N_3O$ $[M+H]^+$ 252.1092, found 252.1104.

4-(naphthalen-1-yl)-1-phenyl-1H-1,2,3-triazole (**3t**): brown yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 9.4 Hz, 1H), 8.27 (s, 1H), 7.93 (d, *J* = 8.5 Hz, 2H), 7.87 (d, *J* = 7.8 Hz, 2H), 7.82 (d, *J* = 7.0 Hz, 1H), 7.64–7.52 (m, 5H), 7.49 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.58, 136.02, 132.89, 130.13, 128.85, 128.19, 127.86, 127.51, 126.57, 126.42, 125.78, 125.09, 124.37, 124.33, 119.60; HRMS (ESI) m/z calcd for $C_{18}H_{13}N_3$ $[M+H]^+$ 272.1143, found 272.1154.

4-(naphthalen-2-yl)-1-phenyl-1H-1,2,3-triazole (**3u**): light brown yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.33 (s, 1H), 8.04–7.98 (m, 1H), 7.97–7.90 (m, 2H), 7.90–7.81 (m, 3H), 7.61–7.45 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.95, 132.53, 132.24, 128.81, 127.83, 127.68, 127.24, 126.79, 126.52, 125.53, 125.29, 123.66, 122.82, 119.57; HRMS (ESI) m/z calcd for $C_{18}H_{13}N_3$ $[M+H]^+$ 272.1143, found 272.1147.

4-(biphenyl-4-yl)-1-phenyl-1H-1,2,3-triazole (**3v**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.00 (d, *J* = 8.3 Hz, 2H), 7.82 (d, *J* = 7.8 Hz, 2H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.8 Hz, 2H), 7.47 (t, *J* = 7.7 Hz, 3H), 7.38 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 128.80, 127.83, 127.82, 126.00, 126.50, 126.00, 125.24, 119.54, 117.48, 116.57; HRMS (ESI) m/z calcd for $C_{18}H_{13}N_3$ $[M+H]^+$ 298.1300, found 298.1327.

4-(furan-2-yl)-1-phenyl-1H-1,2,3-triazole (**3w**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.78 (d, *J* = 8.1 Hz, 2H), 7.55 (t, *J* = 7.7 Hz, 2H), 7.47 (dd, *J* = 13.3, 5.7 Hz, 2H), 6.94 (d, *J* = 3.3 Hz, 1H), 6.53 (dd, *J* = 3.2, 1.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.83, 141.30, 140.11, 135.82, 128.80, 127.88, 119.51, 116.06, 110.58, 106.16; HRMS (ESI) m/z calcd for $C_{12}H_9N_3O$ $[M+H]^+$ 212.0779, found 212.0787.

1-phenyl-4-(thiophen-2-yl)-1H-1,2,3-triazole (**3x**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.78 (d, *J* = 7.9 Hz, 2H),

7.55 (t, *J* = 7.7 Hz, 2H), 7.47 (dd, *J* = 12.5, 5.0 Hz, 2H), 7.35 (dd, *J* = 5.1, 0.9 Hz, 1H), 7.12 (dd, *J* = 5.0, 3.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.91, 135.86, 131.42, 128.79, 127.89, 126.72, 124.39, 123.55, 119.54, 116.07; HRMS (ESI) m/z calcd for $C_{12}H_9N_3S$ $[M+H]^+$ 228.0551, found 228.0583.

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Notes and references

1 (a) A. V. Gulevich, A. S. Dudnik, N. Chernyak, V. Gevorgyan, *Chem. Rev.* 2013, **113**, 3084; (b) S. Chuprakov, S. W. Kwok, V. V. Fokin, *J. Am. Chem. Soc.*, 2013, **135**, 4652; (c) J. E. Spangler, H. M. L. Davies, *J. Am. Chem. Soc.*, 2013, **135**, 6802; (d) M. Zibinsky, V. V. Fokin, *Angew. Chem., Int. Ed.*, 2013, **52**, 1507; (e) K. F. Donnelly, A. Petronilho, M. Albrecht, *Chem. Commun.*, 2013, **49**, 1145; (f) T. C. Johnson, W. G. Totty, M. Wills, *Org. Lett.*, 2012, **14**, 5230.

2 (a) P. Thirumurugan, D. Matosiuk, K. Jozwiak, *Chem. Rev.*, 2013, **113**, 4905; (b) J. C. Jewett, C. R. Bertozzi, *Chem. Soc. Rev.*, 2010, **39**, 1272; (c) M. F. Debets, S. S. van Berkel, J. Dommerholt, A. J. Dirks, F. P. J. T. Rutjes, F. L. van Delft, *Acc. Chem. Res.*, 2011, **44**, 805.

3 (a) P. L. Golas, K. Matyjaszewski, *Chem. Soc. Rev.*, 2010, **39**, 1338; (b) A. Qin, J. W. Y. Lam, B. Z. Tang, *Chem. Soc. Rev.*, 2010, **39**, 2522; (c) H. Wamhoff, In Comprehensive Heterocyclic Chemistry, A. R. Katritzky, C. W. Rees, Pergamon, Oxford, 1984, Vol. 5, pp. 669; (d) S. T. Abu-Orabi, M. A. Atfah, I. Jibril, F. M. Mari'i, A. A. Ali, *J. Heterocycl. Chem.*, 1989, **26**, 1461.

4 (a) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057; (b) A. K. Feldman, B. Colasson, V. V. Fokin, *Org. Lett.*, 2004, **6**, 3897; (c) F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.*, 2005, **127**, 210; (d) B. Chattopadhyay, C. I. R. Vera, S. Chuprakov, V. Gevorgyan, *Org. Lett.*, 2010, **12**, 2166; (e) S. W. Kwok, J. R. Fotsing, R. J. Fraser, V. O. Rodionov, V. V. Fokin, *Org. Lett.*, 2010, **12**, 4217.

5 (a) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 565; (b) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 633; (c) R. Huisgen, R. Knorr, L. Mcius, G. Szeimies, *Chem. Ber.*, 1965, **98**, 4014.

6 H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004.

7 C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057.

8 (a) L. Zhang, X. Chen, P. Xue, H. H. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, G. Jia, *J. Am. Chem. Soc.*, 2005, **127**, 15998; (b) J. Zhang, J. Kemmink, D. T. S. Rijkers, R. J. Liskamp, *Chem. Commun.*, 2013, **49**, 4498.

9 S. Ding, G. Jia, J. Sun, *Angew. Chem., Int. Ed.*, 2014, **53**, 1877.

10 J. Barluenga, C. Valdés, G. Beltrán, M. Escribano, F. Aznar, *Angew. Chem., Int. Ed.*, 2006, **45**, 6893.

11 For a timely highlight on organocatalytic azide-carbonyl [3+2] cycloaddition toward 1,2,3-triazole synthesis, see: S. S. V. Ramasastry, *Angew. Chem., Int. Ed.*, 2014, **53**, 14310.

12 (a) D. B. Ramachary, K. Ramakumar, V. V. Narayana, *Chem. - Eur. J.*, 2008, **14**, 9143; (b) M. Belkheira, D. E. Abed, I. -M. Pons, C. Bressy, *Chem. - Eur. J.*, 2011, **17**, 12917; (c) L. J. T. Danence, Y. Gao, M. Li, Y. Huang, J. Wang, *Chem. - Eur. J.*, 2011, **17**, 3584; (d) D. B. Ramachary, A. B. Shashank, S. Karthik, *Angew. Chem., Int. Ed.*, 2014, **53**, 10420; (e) W. Li, Q. Jia, Z. Du, J. Wang, *Chem. Commun.*, 2013, **49**, 10187; (f) D. B. Ramachary, A. B. Shashank, *Chem. - Eur. J.*, 2013, **19**, 13175; (g) L. Wang, S. Peng, L. J. T. Danence, Y. Gao, J. Wang, *Chem. - Eur. J.*, 2012, **18**, 6088; (h) D. K. J. Yeung, T. Gao, J. Huang, S. Sun, H. Guo, J. Wang, *Green Chem.*, 2013, **15**, 2384; (i) W. Li, Z. Du, J. Huang, Q. Jia, K. Zhang, J. Wang, *Green Chem.*, 2014, **16**, 3003.

13 J. Thomas, J. John, N. Parekh, W. Dehaen, *Angew. Chem., Int. Ed.*, 2014, **53**, 10155.

14 W. Li, J. Wang, *Angew. Chem., Int. Ed.*, 2014, **53**, 14186.

15 Z. K. Chen, Q. Q. Yan, Z. X. Liu, Y. M. Xu, Y. H. Zhang, *Angew. Chem., Int. Ed.* 2013, **52**, 13324.

16 (a) K. Sakai, N. Hida, K. Konde, *Bull. Chem. Soc. Jpn.* 1986, **59**, 179. (b) S. S. van Berkel, S. Brauch, L. Gabriel, M. Henzi, S. Stark, D. Vasilev, L. A. Wessjohann, M. Abbas, B. Westermann, *Angew. Chem., Int. Ed.* 2012, **51**, 5343.

17 S. S. V. Ramasastry, *Angew. Chem., Int. Ed.* 2014, **53**, 14310.

18 H. W. Bai, Zh. J. Cai, Sh. Y. Wang, Sh. J. Ji, *Org. Lett.* 2015, **17**, 2898.

19 Cai, Z.-J.; Lu, X.-M.; Zi, Y.; Yang, C.; Shen, L.-J.; Li, J.; Wang, S.-Y.; Ji, S.-J. *Org. Lett.* 2014, **16**, 5108.

20 For reviews of microreactor technology, see: (a) C. Wiles, P. Watts, *Green Chem.,* 2012**, 14**, 38. (b) C. Wiles; P. Watts, *Chem. Commun.,* 2011, **47**, 6512. (c) J. i. Yoshida, A. Nagaki, T. Yamada, *Chem. Eur. J.,* 2008, **14**, 7450. (d) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.,* 2007, **107**, 2300.

21 J. J. Gu, Zh. Fang, Ch. K. Liu, Zh. Yang, X. Li, P. Wei, K. Guo, *RSC Adv.*, 2015, **5**, 95014.

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A new method for the formation of 1,4-disubstituted 1,2,3-triazoles in continuous flow system under metal- and azide-free conditions has been developed. And the corresponding products were obtained in moderate to good yields.