Metal- and Base-Free Three-Component Reaction of Ynones, Sodium Azide, and Alkyl Halides: Highly Regioselective Synthesis of 2,4,5-Trisubstituted 1,2,3-*NH*-Triazoles

Jihui Li,[a,b] Yuanqing Zhang,[a,b] Dong Wang,[a,b] Wen Wang,[a,b] Tingting Gao,[a,b] Lu Wang,[a,b] Jiting Li,[c] Guosheng Huang,[a,b] Baohua Chen*[a,b]

[a] State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Gansu Lanzhou 730000, P. R. of China

[b] Key Laboratory of Nonferrous Metal Chemistry and Resources Utilization of Gansu Province, Lanzhou University, Gansu Lanzhou 730000, P. R. of China
Fax +86(9319)8912582; E-mail: chbh@lzu.edu.cn

[c] College of Chemical Engineering, Northwest Minoritise University, Gansu Lanzhou 730030, P. R. of China

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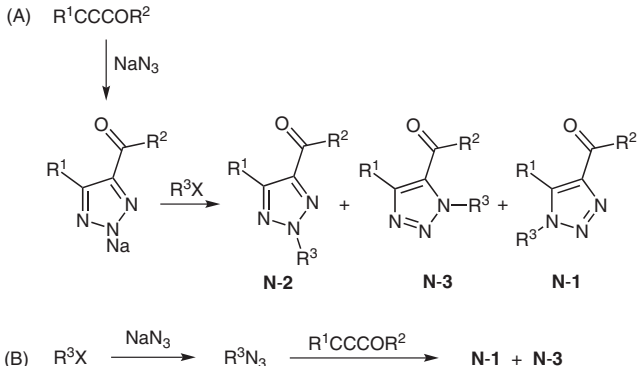
Abstract: A base- and metal-free three-component reaction of ynones, sodium azide, and alkyl halides is developed for the regioselective synthesis of 2,4,5-trisubstituted-1,2,3-triazoles. The method is general, convenient, environmentally benign, atom-economical, and high-yielding.

Key words: 2,4,5-trisubstituted 1,2,3-*NH*-triazole, three-component reaction, green chemistry, click chemistry

1,2,3-Triazoles have become one of the most useful heterocycles because of their biological properties[1] and wide applications in many research fields.[2] By now, there are many methods developed for the synthesis of 1,2,3-triazoles.[3] The classical method is the Huisgen 1,3-dipolar cycloaddition between organic azides and terminal alkynes, but this method is only useful for the synthesis of N1-substituted 1,2,3-triazoles and has other disadvantages.[4] Recently, several approaches have been developed for the synthesis of N2-substituted 1,2,3-triazoles. For examples, Yamamoto and co-workers reported that Pd(0)–Cu(I) catalyzed three-component coupling reaction between alkynes, allyl methyl carbonate, and $TMSN_3$ afforded 2,4-disubstituted 1,2,3-triazoles,[5a] Shi and Wang described the substituted reaction between 1,2,3-triazoles and alkyl halides for the synthesis of 2,4,5-trisubstituted 1,2,3-triazoles.[5b–d] However, these methodologies need stoichiometric amount of bases or metal catalysts. Thus, it is highly desirable to devise novel, base- and catalyst-free and highly selective methods for synthesizing N2-substituted 1,2,3-triazoles concerning environment friendliness and atom economy.

Herein, we describe a novel and operationally simple strategy for the regioselective construction of 2,4,5-trisubstitued 1,2,3-triazoles via three-component reaction of ynones, sodium azide, and alkyl halides under metal- and base-free conditions.

Inspired by our previous work on the synthesis of 4,5-disubstituted 1,2,3-triazoles through the reaction of acid chlorides, terminal acetylenes, and sodium azide,[6] it was envisaged that reaction of ynones, sodium azide, and akyl halides might selectively produce 2,4,5-trisubstitued 1,2,3-triazoles. Hence, we carried out the experiment by mixing 1,3-diphenylprop-2-yn-1-one, sodium azide, and benzyl bromide in DMSO together at room temperature for three hours, a mixture of **1a/2a/3a** (ratio: 9.3:1.0:1.7) trisubstituted 1,2,3-triazoles was obtained in 60% yield after column chromatography (Table 1, entry 1).[7]



Scheme 1 Two parallel cascade reactions of ynones, sodium azide, and alkyl halides

It was found that two parallel reactions of ynones, sodium azide, and alkyl halides proceeded at the same time during the reaction (Scheme 1, A and B), and the reaction B did not produce any N2-substituted 1,2,3-triazole. To suppress the side reaction B, the 1,3-dipolar cycloaddition reaction between 1,3-diphenylprop-2-yn-1-one and sodium azide was carried out first until completion (confirmed by TLC analysis). Benzyl bromide was then added and allowed to react with the in situ formed sodium salt for 160 minutes.

As expected this reaction afforded superior total yield without increasing reaction time (Table 1, entry 2, yield 98%, **1a/2a/3a**: 10.5:1.0:2.0). It is evident that the two-step procedure can accelerate the reaction markedly and increase the yield and selectivity. In order to prove it absolutely, we also performed other similar reactions by taking methyl iodide place of benzyl bromide, the consistent

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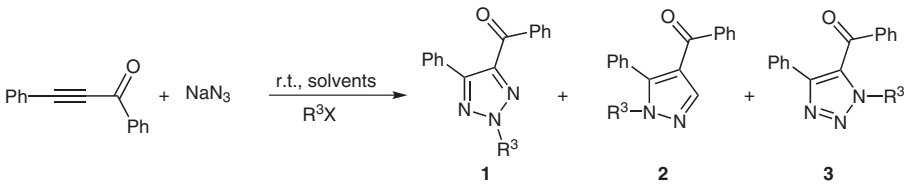
Table 1 Screening Conditions for the Reaction[a]



Entry	R^3X	Solvent	Time (h)	Yield (%)[c]	**1/2/3**[d]	
1[b]	BnBr	DMSO	3	60	**1a/2a/3a**	9.3:1.0:1.7
2	–		3	98	**1a/2a/3a**	10.5:1.0:2.0
3[b]	MeI		5.5	85	**1b/2b/3b**	5.7:1.0:2.3
4	–		1.5	99	**1b/2b/3b**	10.0:1.0:4.0
5	BnBr	DMF	3	96	**1a/2a/3a**	10.0:1.0:1.8
6	–	acetone	3	63	**1a/2a/3a**	7.6:1.0:1.6
7	–	EtOH	3	5	**1a/2a/3a**	7.0:1.0:2.0

[a] The reactions were carried out with 1,3-diphenylprop-2-yn-1-one (0.25 mmol) and NaN_3 (0.275 mmol) in solvent (1.5 mL) reacting at r.t. for 20 min first, then aliphatic alkyl halides (0.375 mmol) were added to the mixture and the reactions continued.
[b] The reactions were carried out by putting 1,3-diphenylprop-2-yn-1-one (0.25 mmol), NaN_3 (0.275 mmol), and aliphatic alkyl halides (0.375 mmol) in DMSO (1.5 mL) together in one pot.
[c] Isolated yields of the combined **1**, **2**, and **3** after column chromatography.
[d] Ratios after column chromatography.

results were obtained (Table 1, entry 3 and 4). Secondly, the solvent's impact on the reaction was investigated in detail, it was found that the reaction can conduct in several solvents including DMSO, DMF, ethanol, acetone (Table 1, entries 1, 5–7), and the aprotic, polar solvent DMSO is the best for the reaction.

With the optimized conditions in hand, the substrate scope of the aliphatic alkyl halides was investigated through the two-step procedure. As seen in Table 2, various aliphatic alkyl halides can react moderately with sodium azide and 1,3-diphenylprop-2-yn-1-one and produce excellent yields and selectivities under mild reaction conditions. For example, when benzyl chloride was used, the reaction proceeded reasonably at room temperature and afforded 98% yield and 8.7:1.0:2.0 (**1a/2a/3a**) regioselectivity (Table 2, entry 1). While 2-$ClC_6H_4CH_2Cl$ was employed, the reaction was accelerated evidently with increasing regioselectivity compared with benzyl chloride (Table 2, entry 2). The saturated straight-chain aliphatic alkyl halides *n*-BuBr and *n*-$C_5H_{11}Br$ reacted easily and provided good results (Table 2, entries 3 and 4), and the longer straight-chain aliphatic alkyl halides including *n*-$C_{12}H_{25}Br$, *n*-$C_{16}H_{33}Cl$, *n*-$C_{16}H_{33}Br$ proceeded sluggishly and gave better regioselectivities, which is mainly caused by their poor solubility and steric efficiency (Table 2, entries 7–9).

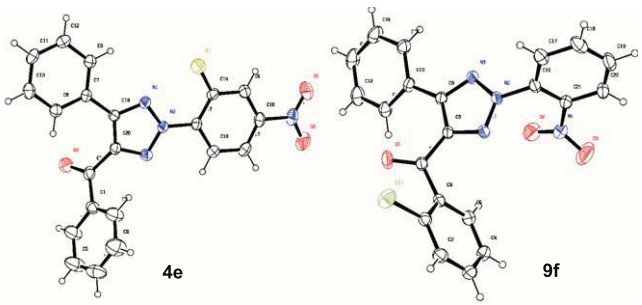
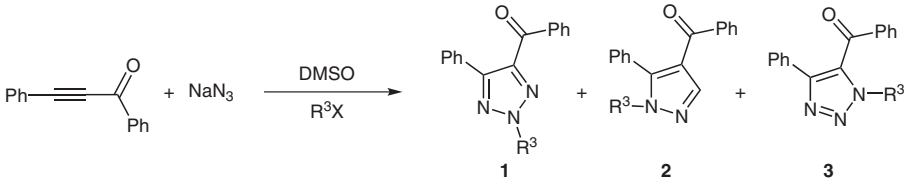


Figure 1 X-ray crystal structures of **4f** and **9e**[8]

The saturated branched chain *s*-BuBr and *i*-$C_5H_{11}Br$ were also investigated. They reacted as well as the corresponding straight-chain aliphatic alkyl bromides under appropriate conditions (Table 2, entries 5 and 6). Importantly, the unsaturated aliphatic alkyl bromides including 3-bromoprop-1-ene and 3-bromoprop-1-yne were also suitable for the procedure (Table 2, entries 10 and 11). Moreover, 1,2-dichloroethane and ethyl 2-bromoacetate can produce good yields and selectivities under indicated reaction conditions (Table 2, entries 12 and 13). Notably, the procedure can accommodate many functional groups that are very useful for the synthesis of correlative derivatives.

Encouraged by these results, we turned our attentions to aryl halides. Interestingly, when the strongly electron-withdrawing nitro group was in the 2- or 4-position of phenyl halides, the reactions proceeded smoothly at higher temperature and only afforded corresponding 2,4,5-trisubstituted 1,2,3-triazoles in good yields (Table 3, entries 1, 2–4, and 6). Moreover, the aryl chlorides bearing two electron-withdrawing groups could accelerate the reactions greatly and converted into the corresponding N2-substituted 1,2,3-triazoles with highly good yields (Table 3, entries 8 and 11). The heterocyclic 2-Cl-3-O_2N-pyridine was also suitable for the reaction and only yielded the desired N2-substituted 1,2,3-triazoles in 94% yield (Table 3, entry 9). However, as 3-$O_2NC_6H_4Cl$,

Table 2 Substrate Scope of Aliphatic Alkyl Halides[a]



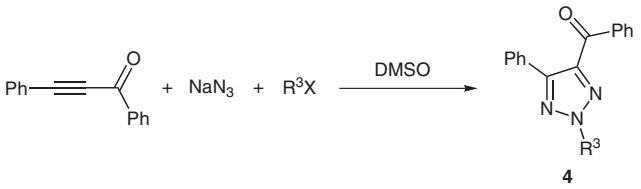
Entry	R^3X	Time (h)	Yield (%)[b]	**1/2/3**[c]	
1	BnCl	16	98	**1a/2a/3a**[9]	8.7:1.0:2.0
2	2-$ClC_6H_4CH_2Cl$	7	98	**1c/2c/3c**	19.0:1.0:2.5
3	*n*-BuBr	4	76 (**1d**)[e]		
4	*n*-$C_5H_{11}Br$	6	98	**1e/2e/3e**	16.5:1.0:2.5
5	*i*-$C_5H_{11}Br$	12	85 (**1f**)[e]		
6[d]	*s*-BuBr	30	87 (**1g**)[e]		
7	*n*-$C_{12}H_{25}Br$	7	96	**1h/2h/3h**	21.0:1.0:2.5
8[f]	*n*-$C_{16}H_{33}Cl$	40	97	**1i/2i/3i**	20.0:1.0:2.8
9	*n*-$C_{16}H_{33}Br$	60	96	**1i/2i/3i**	20.0:1.0:2.0
10	propen-3-yl	6	98	**1j/2j/3j**	6.6:1.0:1.7
11	propyn-3yl	2	98	**1k/2k/3k**	12.3:1.0:2.7
12[g]	DCE	50	65 (**1l**)[e]		
13	$BrCH_2COOMe$	6	73 (**1m**)[e]		

[a] The reactions were carried out with 1,3-diphenylprop-2-yn-1-one (0.25 mmol) and sodium azide (0.275 mmol) in DMSO (1.5 mL) reacting at r.t. for 20 min first, then aliphatic alkyl halides (0.375 mmol) were added to the mixture and the reactions continued.
[b] Isolated yields of the combined **1**, **2**, and **3** after column chromatography.
[c] Ratios after column chromatography.
[d] The reaction temperature was 50 °C.
[e] Yields of **1** after column chromatography.
[f] After 1-chlorohexadecane was added, the reaction temperature was improved to 80 °C.
[g] The reactions were carried out with 1,3-diphenylprop-2-yn-1-one (0.25 mmol) and NaN_3 (0.275 mmol) in DMSO (1 mL) reacting for 20 min at 50 °C first, then DCE (0.5 mL) was added to the mixture and continued the reaction at 50 °C.

2-NCC_6H_4Cl and 4-MeC_6H_4Cl were used, the yields decreased sharply (Table 3, entries 5, 7, and 10). Gratifyingly, when the substrate was extended to 3,4-di$FC_6H_4NO_2$, the coupling step mainly took place at 4-position of 3,4-di$FC_6H_3NO_2$ and generated the corresponding 2,4,5-trisubstitued 1,2,3-triazoles **4f** with 93% isolated yield in shorter time (Table 3, entry 12). The structure of **4f** was confirmed by X-ray crystallography (Figure 1, **4f**). As 2,5-di-F-$C_6H_3NO_2$ and 2,5-di-Br-$C_6H_3NO_2$ were employed, the reactions alternatively proceeded at 2-position of them and yielded the corresponding 2,4,5-trisubstituted 1,2,3-triazoles with 94% and 88% yields, respectively (Table 3, entries 13 and 14). It may be deduced that the electronic properties of aryl halides have a strong influence on the reaction.

Finally, using both aryl halides (**5**: 2,5-di$FC_6H_3NO_2$, **6**: 2-$O_2NC_6H_4Cl$, **7**: 2-$ClC_6H_4CH_2Cl$, **8**: 4-$O_2NC_6H_4Cl$) and aliphatic alkyl halide (7) as coupling reagents, the scope of ynones was examined (Table 4). Consistent with the above results, various ynones could react moderately with halides, and produced 2,4,5-trisubstituted 1,2,3-triazoles in excellent yields. For example, when the aryl-disubstituted ynones whose aryl R^2 are electron-poor or electron-rich were employed, they reacted as well as that diphenylprop-2-yn-1-one was used (entries 1–15). The aryl-disubstituted yones of which the aryl R^1 are electron-poor or electron-rich also produced the excellent results (Table 4, entries 18–21). When 1-(furan-2-yl)-3-phenylprop-2-yn-1-one was used, the reactions yielded the desired N2-substituted product in good yields (Table 4, entries 16 and 17). Interestingly, the reaction of 1-phenylhept-2-yn-1-one, sodium azide, and 1,4-difluoro-2-nitrobenzene produced product 9v in only 60% yield and another isomer which may be caused by the steric and electronic properties of the substrates (Table 4, entry 22), whereas the reaction between 1-phenylhept-2-yn-1-one, sodium azide, and 1-chloro-2-nitrobenzene only afforded the corresponding 2,4,5-trisubstituted 1,2,3-triazole 9w with 95% yield. In addition, 1-phenyl-3-ferrocenylprop-2-yn-1-one and 1-phenyl-3-(thiophen-3-yl)prop-2-yn-1-one were efficient

Table 3 Substrate Scope of Aryl Halides[a]



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Entry	R^3X	Time (h)	Temp (°C)	Yield of **4** (%)[b]	
1	4-$O_2NC_6H_4Cl$	48	120	**4a**	85
2	2-$ON_2C_6H_4F$	8	100	**4b**	97
3	4-$ON_2C_6H_4I$	36	120	**4a**	85
4	2-$O_2NC_6H_4Cl$	36	120	**4b**	90
5	4-MeC_6H_4Cl	3	120		0
6	2-$O_2NC_6H_4Cl$	36	120	**4b**	90
7	3-$O_2NC_6H_3Cl$	36	120		0
8	2-NC-4-$O_2NC_6H_4Cl$	9	120	**4c**	97
9	2-Cl-3-O_2N-pyridine	12	120	**4d**	94
10	2-NCC_6H_4Cl	36	120		trace
11	2,4-di$O_2NC_6H_3Cl$	8	120	**4e**	96
12	3,4-di$FC_6H_3NO_2$	3	100	**4f**	93[c]
13	2,5-di$FC_6H_3NO_2$	3	100	**4g**	94
14	2,5-di$BrC_6H_3NO_2$	3	100	**4h**	88

[a] The reactions were carried out by putting 1,3-diphenylprop-2-yn-1-one (0.25 mmol), NaN_3 (0.25 mmol), and aryl halides (0.375 mmol) in DMSO (1.5 mL) together in one pot.
[b] Isolated yields after column chromatography.
[c] Confirmed by X-ray crystallography (see Figure 1, **4f**).

with excellent yields and regioselectivities (Table 4, entries 24–27).

It is revealed that the regioselectivities of using aryl halides as coupling reagent are better than when using aliphatic alkyl halides due to the steric effect of alkyl halides.

In summary, we have developed a novel, metal- and base-free three-component reaction of simple raw materials ynones, sodium azide, and alkyl halides for regioselectively synthesizing 2,4,5-trisubstitued 1,2,3-triazoles. The procedure is efficient, convenient, environmentally friendly, and atom-economical. A variety of substrates are suitable for the method and even 3,4-di$FC_6H_3NO_2$, 2,5-di$FC_6H_3NO_2$, and 2,5-di$BrC_6H_3NO_2$ can also produce excellent results. Further studies on regioselective synthesis of 1,2,3-triazoles are under investigation in our group.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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References

(1) (a) Al-Masoudim, N. A.; Al-SoudY, A. *Tetrahedron Lett.* **2002**, *43*, 4021. (b) Alvarez, R.; Velazquez, S.; Aquaro, A.; San-Felix, S.; Clercq, E. D.; Perno, C.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185. (c) Wamhoff, H. In *Comprehensive Heterocyclic Chemistry*, Vol. 5; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon: Oxford, **1984**, 669. (d) Buckle, D. R.; Rockell, C. J. M.; Smith, H.; Spicer, B. A. *J. Med.Chem.* **1986**, *29*, 2262. (e) Buckel, D. R.; Outred, D. J.; Rockell, C. J. M.; Smith, H.; Spicer, B. A. *J. Med. Chem.* **1983**, *26*, 251. (f) Holla, B. S.; Mahalinga, M.; Karthikeyan, M. S.; Poojary, B.; Akberali, P. M.; Kumari, N. S. *Eur. J. Med. Chem.* **2005**, *40*, 1173. (g) Olesen, P. H.; Sørensen, A. R.; Ursø, B.; Kurtzhals, P.; Bowler, A. N.; Ehrbar, U.; Hansen, B. F. *J. Med. Chem.* **2003**, *46*, 3333.

(2) (a) Wacharasindhu, S.; Bardhan, S.; Wan, Z.-K.; Tabei, K.; Mansour, T. S. *J. Am. Chem. Soc.* **2009**, *131*, 4174. (b) Bock, V. D.; Speijer, D.; Hiemstra, H.; Maarseveen, J. H. V. *Org. Biomol. Chem.* **2007**, *5*, 971. (c) Costa, M. S.; Boechat, N.; Rangel, E. A.; Silva, F. D. D.; Souza, A. M. T. D.; Rodrigues, C. R.; Castro, H. C.; Junior, I. N.; Lourenco, M. C. S.; Wardell, S.; Ferreira, V. F. *Bioorg. Med. Chem.* **2006**, *14*, 8644. (d) Sivakumar, K.; Xie, F.; Cash, B. M.; Long, S.; Barnhill, H. N.; Wang, Q. *Org. Lett.* **2004**, *6*, 4603. (e) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128. (f) Manetsch, R.; Krasiski, A.; Radi, Z.; Raushel, J.; Taylor, P. K.; Sharpless, B.; Kolb, H. C. *J. Am. Chem. Soc.* **2004**, *126*, 12809.

(3) Selected examples of methods of synthesizing 1,2,3 triazoles: (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596. (b) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998. (c) Yang, D.; Fu, N.; Liu, Z.; Li, Y.; Chen, B. *Synlett* **2007**, 278. (d) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (e) Chen, Z.-Y.; Wu, M.-J. *Org. Lett.* **2005**, *7*, 475. (f) Sreedhar, B.; Reddy, P. S.; Krishna, V. R. *Tetrahedron Lett.* **2007**, *48*, 5831. (g) Coats, S. J.; Link, J. S.; Gauthier, D.; Hlasta, D. J. *Org. Lett.* **2005**, *7*, 1469.

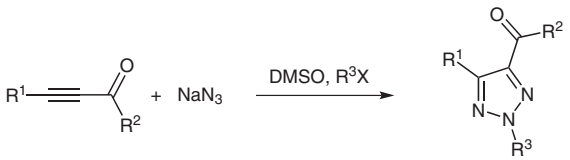
(4) (a) Hlasta, D. J.; Ackerman, J. H. *J. Org. Chem.* **1994**, *59*, 6184. (b) Sasaki, T.; Eguchi, S.; Yamaguchi, M.; Esaki, T. *J. Org. Chem.* **1981**, *46*, 1800. (c) Howell, S. J.; Spencer, N.; Philp, D. *Tetrahedron* **2001**, *57*, 4945. (d) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297.

(5) Recent developed methods of synthesizing N2-substitued 1,2,3 triazoles: (a) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7786. (b) Chen, Y.; Liu, Y.; Petersena, J. L.; Shi, X. *Chem. Commun.* **2008**, 3254. (c) Liu, Y.; Yan, W.; Chen, Y.; Petersen, J. L.; Shi, X. *Org. Lett.* **2008**, *10*, 5389. (d) Wang, X.; Zhang, L.; Lee, H.; Haddad, N.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2009**, *11*, 5026. (e) Kalisiak, J.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2008**, *10*, 3171.

(6) Li, J.; Wang, D.; Zhang, Y.; Li, J.; Chen, B. *Org. Lett.* **2009**, *11*, 3024.

(7) Three isomers can be readily isolated by column chromatography. According to the ref. 5b, N2-alkylation of 4,5-disubstituted 1,2,3-triazoles is the most favorable and the

Table 4 Substrate Scope of Ynones[a]



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Entry	R^1	R^2	R^3X		Yield of **9** (%)[b]	
1	Ph	4-ClC_6H_4	**5**	2,5-di$FC_6H_4NO_2$	**9a**	95
2[c]	–	–	**7**	2-$ClC_6H_4CH_2Cl$	**9b**	86
3	–	3-ClC_6H_4	**5**	2,5-di$FC_6H_4NO_2$	**9c**	94
4[c]	–	–	**7**	2-$ClC_6H_4CH_2Cl$	**9d**	85
5[d]	–	2-ClC_6H_4	**5**	2,5-di$FC_6H_4NO_2$	**9e**	97[f]
6[c]	–	–	**7**	2-$ClC_6H_4CH_2Cl$	**9f**	87
7[e]	–	3-MeC_6H_4	**8**	4-$O_2NC_6H_4Cl$	**9g**	92
8[c]	–	–	**7**	2-$ClC_6H_4CH_2Cl$	**9h**	86
9	–	3,5-diMeC_6H_4	**5**	2,5-di$FC_6H_4NO_2$	**9i**	97
10[c]	–	–	**7**	2-$ClC_6H_4CH_2Cl$	**9j**	90
11	–	4-MeOC(O)C_6H_4	**5**	2,5-di$FC_6H_4NO_2$	**9k**	93
12	–	4-$MeOC_6H_4$	**5**	2,5-di$FC_6H_4NO_2$	**9l**	94
13[c]	–	–	**7**	2-$ClC_6H_4CH_2Cl$	**9m**	82
14	–	4-$O_2NC_6H_4$	**5**	2,5-di$FC_6H_4NO_2$	**9n**	95
15[c]	–	–	**7**	2-$ClC_6H_4CH_2Cl$	**9o**	85
16	–	furan-2-yl	**5**	2,5-di$FC_6H_4NO_2$	**9p**	93
17[c]	–	–	**7**	2-$ClC_6H_4CH_2Cl$	**9q**	82
18	4-$MeOC_6H_4$	Ph	**5**	2,5-di$FC_6H_4NO_2$	**9r**	96
19[c]	–	–	**7**	2-$ClC_6H_4CH_2Cl$	**9s**	83
20	4-FC_6H_4	–	**5**	2,5-di$FC_6H_4NO_2$	**9t**	95
21[c]	–	–	**7**	2-$ClC_6H_4CH_2Cl$	**9u**	84
22	*n*-Bu	–	**5**	2,5-di$FC_6H_4NO_2$	**9v**	60
23[d]	–	–	**6**	2-$O_2NC_6H_4Cl$	**9w**	95
24	Fc	–	**5**	2,5-di$FC_6H_4NO_2$	**9x**	97
25[c]	–	–	**7**	2-$ClC_6H_4CH_2Cl$	**9y**	88
26	thiophen-3-yl	–	**5**	2,5-di$FC_6H_4NO_2$	**9z**	98
27[c]	–	–	**7**	2-$ClC_6H_4CH_2Cl$	**9a′**	88

[a] The reactions were carried out by putting ynones (0.25 mmol), NaN_3 (0.25 mmol), and aryl halides (0.375 mmol) in DMSO (1.5 mL) at 100 °C.
[b] Isolated yields after column chromatography.
[c] The reactions were carried out with ynones (0.25 mmol) and NaN_3 (0.275 mmol) in DMSO (1.5 mL) reacting for 20 min at r.t. first, then aliphatic alkyl halides (0.375 mmol) were added to the mixture and continued the reaction for 24 h at r.t.
[d] The reaction time was 40 h, and the temperature was 120 °C.
[e] The reaction time was 36 h, and the temperature was 120 °C.
[f] Confirmed by X-ray crystallography (see Figure 1, **9e**).

polarity of N2 product is the lowest. Additionally, N1-alkylation was the least favored in almost all cases due to the conformation of 1,4,5-trisubstituted 1,2,3-triazoles. Therefore, we can distinguish the **N-1**, **N-2**, and **N-3** products easily.

(8) The CCDC number of **4f** ($C_{21}H_{13}FN_4O_3$): 752728, the CCDC number of **9e** ($C_{21}H_{13}ClN_4O_3$): 752729.

(9) **Regioselective Synthesis of 2,4,5-Trisubstituted 1,2,3-Triazoles – General Procedure for the Reaction between Ynones, Sodium Azide, and Aliphatic Alkyl Halides, Regioselective Sythesis of (2-Benzyl-5-phenyl-2*H*-1,2,3-triazol-4-yl)(phenyl)methanone (1a)**

All reactions were performed on a 0.25 mmol scale relative to ynones. 1,3-Diphenylprop-2-yn-1-one (0.25 mmol), NaN_3 (0.275 mmol) and DMSO (1.5 mL) were successively added to a round-bottom sidearm flask (10 mL) reacted at r.t. until ynones disappeared by TLC test (about 20 min), then benzyl bromide (0.375 mmol) was added to the mixture and the reaction continued at r.t. for 160 min. Following, to the reaction mixture was added H_2O (2 mL), 20% HCl solution (1 mL), and extracted with ester (3 × 10 mL). The combined organic phases were washed with brine (2 × 3 mL), dried over anhyd $MgSO_4$, and concentrated in vacuo. The residue was subjected to flash column chromatography with hexanes–EtOAc (40:1, 20:1, 5:1) as eluent to obtain the desired isomers **1a** (**1a**: 63mg), **2a** (6 mg), **3a** (12 mg), 98% yield.

(2-Benzyl-5-phenyl-2*H*-1,2,3-triazol-4-yl)(phenyl)-methanone (1a)

Mp 93–95 °C. IR: 3063.48, 1661.58, 1597.39 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.03–8.06 (m, 2 H), 7.79–7.82 (m, 2 H), 7.56–7.61 (m, 1 H), 7.35–7.48 (m, 10 H), 5.68 (s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.84, 150.01, 142.24, 137.25, 134.47, 133.30, 130.44, 129.61, 129.07, 128.86, 128.71, 128.60, 128.32, 128.27, 128.17, 59.24. HRMS: *m/z* calcd for $C_{22}H_{18}N_3O$ $[M + H]^+$: 340.14444; found: 340.14426.[5b]

General Procedure of the Reaction between Ynones, Sodium Azide, and Aryl Halides: Regioselective Synthesis of [2-(4-Nitrophenyl)-5-phenyl-2*H*-1,2,3-triazol-4-yl](phenyl) Methanone (2a)

All reactions were performed on a 0.25 mmol scale relative to ynones. 1,3-Diphenylprop-2-yn-1-one (0.25 mmol), NaN_3 (0.25 mmol), 4-$O_2NC_6H_4Cl$ (0.375 mmol), and DMSO (1.5 mL) were successively added to a round-bottom sidearm flask (10 mL) and reacted at 120 °C for 48 h, then H_2O (2 mL), 20% HCl solution (1 mL) were added to the reaction mixture after cooled and extracted with ester (3 × 10 mL). The combined organic phases were washed with brine (2 × 3 mL), dried over anhyd $MgSO_4$, and concentrated in vacuo. The residue was subjected to flash column chromatography with hexanes–EtOAc (20:1) as eluent to obtain the desired **4a** (79 mg, yield 85%); mp 145–147 °C. IR: 3074.59, 2918.34, 1652.74, 1593.64 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.33–8.35 (m, 4 H), 8.11–8.13 (m, 2 H), 7.87–7.90 (m, 2 H), 7.64–7.67 (m, 1 H), 7.44–7.54 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.45, 151.34, 146.89, 144.36, 143.09, 136.65, 133.90, 130.44, 129.82, 128.69, 128.58, 128.56, 128.52, 125.20, 119.50. MS (EI): *m/z* = 370 $[M]^+$. Anal. Calcd for $C_{21}H_{14}N_4O_3$: C, 68.10; H, 3.81; N, 15.13. Found: C, 68.14; H, 3.79; N, 15.15.[6]

Copies of NMR spectroscopic, ESI-HRMS analysis, MS (EI) element analysis, and X-ray crystallography are found in the Supporting Information.