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Facile One-Pot Synthesis of 4,5-Disubstituted 1,2,3-(NH)-Triazoles through Sonogashira Coupling/ 1,3-Dipolar Cycloaddition of Acid Chlorides, Terminal Acetylenes, and Sodium Azide

Jihui Li,[†] Dong Wang,[†] Yuanqing Zhang,[†] Jiting Li,[‡] and Baohua Chen*,[†]

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Gansu Lanzhou 730000, P. R. China, and College of Chemical Engineering, Northwest Minoritise University, Gansu Lanzhou730030, P. R. China

chbh@lzu.edu.cn

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ABSTRACT

A novel and efficient way of synthesizing 4,5-disubstituted-1,2,3-(NH)-triazoles through palladium-catalyzed and ultrasonic promoted Sonogashira coupling/1,3-dipolar cycloaddition of acid chlorides, terminal acetylenes, and sodium azide in one pot is developed. The reaction scope is quite general, and the methodology can produce excellent yields. The regioselective 1,4,5-trisubstituted-1,2,3-(NH)-triazoles can be made easily from 4,5-disubstituted-1,2,3-(NH)-triazoles.

During the last decades, 1,2,3-triazoles have become one of the best synthesized classes for chemists as they display many interesting properties including antibacterial,[1] herbicidal, fungicidal,[2] antiallergic,[3] anti-HIV,[4] GSK-3 inhibiting,[5] and antineoplastic activities.[6] Moreover, they have been widely used in various research fields, including biological science,[7] material chemistry,[8] medicinal chemistry,[9] and synthetic organic chemistry.[10]

Many methods have been developed to synthesize 1,2,3-triazoles by now.[11] Traditionally, the Huisgen 1,3-dipolar cycloaddition between organic azides and terminal alkynes is a useful and extensively applicable method for the synthesis of N-substituted triazoles. However, the efficiency of this method is dependent on the steric and electronic properties of the alkyne, and the regioselectivities of these

[†] Lanzhou University.
[‡] Northwest Minoritise University.

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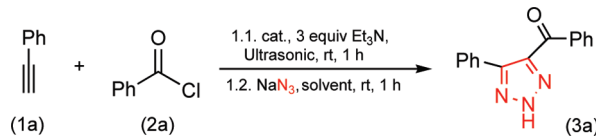
reactions are generally low within unsymmetrical alkynes giving rise to regioisomeric mixtures of triazoles until recently.[12] In addition, the low molecular weight organic azides are sometimes unstable and difficult to handle.[13] Therefore, it is highly desirable to develope more efficient synthetic and operationally simple methodologies used for synthesizing a diverse array of [1,2,3]-triazoles.

Many new methods of synthesizing 1,2,3-triazoles were developed in the past two years inspired by the "click" chemistry and their broad application in many fields.[14] However, most of these developed methods are for N-substituted 1,2,3-triazoles, and only a few are for N-unsubstituted 1,2,3-triazoles which also have wide utilities.[15] Thus, it is very necessary and complementary to find novel ways of synthesizing N-unsubstituted 1,2,3-triazoles in the future. In this paper, an efficient, convenient and safe one-pot procedure was developed to synthesize 4,5-disubstituted-1,2,3-(NH)-triazoles through palladium-catalyzed and ultrasonic promoted Sonogashira coupling/1,3-dipolar cycloaddition of acid chlorides, terminal acetylenes and sodium azide.

Enlightened by the application of Sonogashira coupling in one-pot synthetic organic processes,[16] it was assumed that a three-component reaction of acid chlorides, terminal acetylenes and sodium azide would provide an efficient route for the synthesis of 4,5-disubstituted-1,2,3-(NH)-triazoles. In our starting experiments, where phenyl acetylene, benzoyl chloride, sodium azide were put in one pot with the catalyst of $PdCl_2(PPh_3)_2$ (1 mmol %)/CuI (2 mmol %) and the base Et_3N together in various solution(Et_3N, dioxane, toluene, THF, DMSO), and reacted under nitrogen at room temperature (rt) for 24 h, we only achieved trace of the triazole **3a** and byproducts. In the latter experiments, where phenyl acetylene and benzoyl chloride were catalyzed by $PdCl_2(PPh_3)_2$/CuI and promoted by ultrasonic (32 kHz, 160 W) at rt in advance, followed by NaN_3-1,3-dipolar cycloaddition in DMSO, 4,5-disubstituted-1,2,3-(NH)-triazoles, **3a** was obtained with 98% isolated yield (Table 1, entry 1). The impact of bases, solvents and catalystes was investigated in detail for the reaction (Table 1). When using other bases, the reaction gave low yields (Table 1, entries 2, 3, 4). The reaction can be performed in various solutions including

Table 1. Screening the Impact of Bases, Solutions and Catalysts[a]



(1a) (2a) (3a)

entry	cat.(mmol %)	solvent	base	yield (%)[b]
1	$PdCl_2(PPh_3)_2$(1)/CuI(2)	DMSO	Et_3N	98
2	$PdCl_2(PPh_3)_2$(1)/CuI(2)	DMSO	pyridine	trace
3	$PdCl_2(PPh_3)_2$(1)/CuI(2)	DMSO	diisopropylamine	70
4	$PdCl_2(PPh_3)_2$(1)/CuI(2)	DMSO	tert-butylamine	trace
5	$PdCl_2(PPh_3)_2$(1)/CuI(2)	DMF	Et_3N	92
6	$PdCl_2(PPh_3)_2$(1)/CuI(2)	Dioxane	–	45
7	$PdCl_2(PPh_3)_2$(1)/CuI(2)	Enthanol	–	35
8	$PdCl_2(PPh_3)_2$(1)/CuI(2)	$CHCl_3$	–	40
9	$PdCl_2(PPh_3)_2$(1)/CuI(2)	THF	–	20
10	$PdCl_2(PPh_3)_2$(1)/CuI(2)	acetonitrile	–	30
11	$PdCl_2$(5)	DMSO	–	90
12	Pd/C(5)	DMSO	–	trace
13	CuI(5)	DMSO	–	trace
14	$Pd(PPh_3)_4$(5)	DMSO	–	70
15	$Pd(dba)_2$(5)	DMSO	–	65
16	$PdCl_2(PPh_3)_2$(5)	DMSO	–	trace

[a] The reaction was carried out with **1a** (0.5 mmol), **2a** (0.5 mmol) and Et_3N (3 equiv, 1.5 mmol) in the presence of catalyst promoted by ultrasonic (32 kHz, 160 W) at room temperature for 1 h first under nitrogen, then NaN_3 (1.2 equiv, 0.6 mmol) and 1 mL solvent was added to the mixture and the reaction continued at rt for one more hour. [b] Isolated yields after column chromatography.

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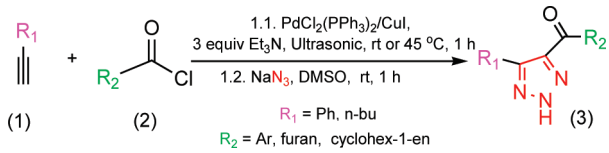
DMSO, DMF, dioxane, enthanol, chloroform, THF, acetonitrile using $PdCl_2(PPh_3)_2$/CuI as catalyst (Table 1, entries 1, 5−10); and the aprotic, polar solvent DMSO is the most favorable for the reaction. When $PdCl_2(PPh_3)_2$/CuI was changed to other catalysts, the yields decreased (Table 1, entries 11, 14, 15) and even trace product was obtained only (Table 1, entries 12, 13, 16) with DMSO as solvent and Et_3N as base. Therefore, the Et_3N, $PdCl_2(PPh_3)_2$/CuI and DMSO is the best system for this reaction.

Encouraged by the efficiency of the reaction protocol described above, the substrate scope was investigated next. A variety of acid chlorides were tested under the optimized conditions using phenylacetylene or hex-1-yne as the coupling agent. It was found that several electron-rich phenyl acid chlorides were suitable substrates for the reaction, affording the corresponding 4,5-disubstituted-1,2,3-(NH)-triazoles in excellent yields (85−99%, Table 2, entries 1, 2,

Table 2. Substrate Scope of Acid Chlorides[a]



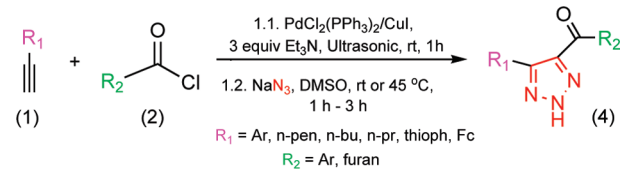
entry	R_1	R_2	product	yield[b]
1	Phenyl	4-CH_3Phenyl	**3b**	99
2	–	3-CH_3Phenyl	**3c**	98
3	–	2-CH_3Phenyl	**3d**	99
4	–	2-ClPhenyl	**3e**	60(93)[c]
5	–	4-ClPhenyl	**3f**	99
6	–	4-NO_2Phenyl	**3g**	83[d]
7	–	4-CH_3OPhenyl	**3h**	85[d]
8	–	3-Cl Phenyl	**3i**	98
9	–	3,5-DiCH_3Phenyl	**3j**	98
10	–	2,6-DiCH_3Phenyl	**3k**	trace
11	–	2,6-DiClPhenyl	**3l**	trace
12	–	funan-2-yl	**3m**	97
13	*n*-butyl	cyclohex-1-enyl	**3n**	88

[a] The reaction was carried out with **1a** (0.5 mmol), **2a** (0.5 mmol) and Et_3N (3 equiv, 1.5 mmol) in the presence of $PdCl_2(PPh_3)_2$ (1 mol %)/CuI (2 mol %) promoted by ultrasonic (32 kHz, 160 W) at room temperature for 1 h first under nitrogen, then NaN_3 (1.2 equiv, 0.6 mmol) and 1 mL DMSO are added to the mixture and the reaction continued at rt for one more hour. [b] Isolated yields after column chromatography. [c] The reaction was carried out with $PdCl_2$ (5 mol %) as a catalyst. [d] The reaction temperature is increased to 45 °C before NaN_3 and DMSO are added.

3, 7, 9). In addition, electron-deficient phenyl acid chlorides provided the coupling/1,3-dipolar cycloaddition products in consistent yields (83−99%, Table 2, entries 4, 5, 6, 8). Even when the acid chloride incorporated strongly an electron-withdrawing nitro group or an electron-rich methoxyl moiety, the reaction also conducted reasonably at higher temperature (Table 2, entries 6, 7). The sterically hindered benzoyl chloride can react completely without yileds decreasing (Table 2, Entries 3, 4). While the more sterically hindered benzoyl chloride only gave trace products (Table 2, entries 10, 11). When heterocycle furan-2-carbonyl chloride was employed, the reaction can conduct moderately since benzoyl chloride is used (Table 2, entry 12). The reaction of the aliphatic cyclohex-1-enecarbonyl chloride and hex-1-yne can also produce good yiled (Table 2, entry 13).

The scope of the process related to other kinds of terminal acetylenes was also examined (Table 3). When other kinds

Table 3. Substrate Scope of Terminal Acetylenes[a]



entry	R_1	R_2	product	yield (%)[b]
1	4-CH_3OPhenyl	Phenyl	**4a**	99
2	–	4-CH_3Phenyl	**4b**	98
3	–	3-Cl Phenyl	**4c**	98
4	–	4-Cl Phenyl	**4d**	98
5	–	3, 5-DiCH_3Phenyl	**4e**	98
6	–	funan-2-yl	**4f**	94
7	4-FPhenyl	Phenyl	**4g**	98
8	*n*-C_4H_9	Phenyl	**4h**	90[c]
9	–	4-CH_3Phenyl	**4i**	94[c]
10	–	2-CH_3Phenyl	**4j**	92[c]
11	–	4-ClPhenyl	**4k**	95[c]
12	–	3-ClPhenyl	**4l**	95[c]
13	–	3,5-DiCH_3Phenyl	**4m**	96[c]
14	*n*-C_5H_{11}	3,5-DiCH_3Phenyl	**4n**	95[c]
15	*n*-C_3H_7	Phenyl	**4o**	88[c]
16	–	3, 5-DiCH_3Phenyl	**4p**	90[c]
17	–	3-ClPhenyl	**4q**	90[c]
18	thiophen-3-yl	4-CH_3Phenyl	**4r**	97
19	–	2-CH_3Phenyl	**4s**	98
20	–	3-ClPhenyl	**4t**	97
21	Fc	4-CH_3Phenyl	**4u**	93
22	–	3,5-DiCH_3Phenyl	**4v**	95

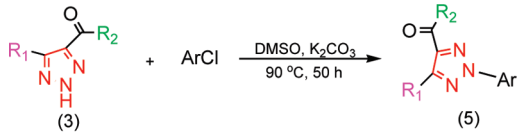
[a] The reaction was carried out with **1a** (0.5 mmol), **2a** (0.5 mmol) and Et_3N (3 equiv, 1.5 mmol) in the presence of $PdCl_2(PPh_3)_2$ (1 mol %)/CuI (2 mol %) promoted by ultrasonic (32 kHz, 160 W) at room temperature for 1 h under nitrogen first, then NaN_3 (1.2 equiv, 0.6 mmol) and 1 mL DMSO was added to the mixture and the reaction continued for one more hour. [b] Isolated yields after column chromatography. [c] The temperature is increased to 45 °C as NaN_3 and DMSO are added, and the reaction continued for another three hours.

of terminal acetylenes were employed, it was found that they are efficient with very high yields when using phenyl acetylene. For example, 4-methoxyl phenyl acetylene can react with several phenyl acid chlorides or furan-2-carbonyl chloride to produce excellent results, indicating that the procedure did not depend on the electronic properties of aryl terminal acetylenes and acid chlorides (Table 3, entries 1−6). When aliphatic terminal acetylenes were used, this reaction proceeded completely at proper temperature (rt or 45 °C), and it was much slower than when using aryl terminal acetylene; the chain length of aliphatic terminal acetylenes did not affect the yields (Table 3, entries 7−16). The terminal acetylene was also extended to 3-ethynylthiophene or ethynyl ferrocene (Fc). They can react completely with acid chlorides

when phenyl acetylene is used (Table 3, entries 17−21). Notably, the reaction conditions are compatible with a variety of terminal acetylenes and acid chlorides. Consistent with the previous studies, the electronic properties of the substrates almost do not have any negative impact on the process.

Finally, the coupling of N-unsubstituted triazoles and aryl chlorides was studied with a series of new N-unsubstituted triazoles in hand. To our excitement, when 1-chloro-4-nitrobenzene was used as coupling agent, they can react moderately in DMSO using K_2CO_3 as base and give only N-2 alkylation 1,2,3-(NH)-triazoles (Scheme 1: **5a**, **5b**, **5c**), because the N-2-substituted triazoles are thermodynamically more stable with less steric hindrance.[17] when the coupling agent was changed to other aryl chlorides, no reaction occurred (Scheme 1: **5d**, **5e**, **5f**). It is showed that this reaction is dependent on the electronic properties of aryl chlorides.

Scheme 1. *N*-2-Aryl-1,2,3-triazoles Synthesis



5a: R_1 = Ph, R_2 = Ph, Ar = 4-NO_2Phenyl yield 60%
5b: R_1 = Ph, R_2 = 3.5-diCH_3Ph, Ar = 4-NO_2Phenyl yield 70%
5c: R_1 = n-bu, R_2 = Ph, Ar = 4-NO_2Phenyl yield 85%
5d: R_1 = Ph, R_2 = Ph, Ar = 4-CNPhenyl yield 0
5e: R_1 = Ph, R_2 = Ph, Ar = Phenyl yield 0
5f: R_1 = Ph, R_2 = Ph, Ar = 4-CH_3Phenyl yield 0

In conclusion, we have developed a novel, facile and efficient method for synthesizing 4,5-disubstituted-1,2,3-(NH)-triazoles directly from acid chlorides, terminal alkynes, and sodium azide based on Sonogashira coupling. The procedure is suitable for many substrates and various 4,5-disubstituted-N-unsubstituted 1,2,3-triazoles can be produced with excellent yields conveniently in short time using cheap and easily available starting materials. Especially, the reaction is hardly impacted by the electronic properties of the subtracts, complementary to the classic Huisgen 1,3-dipolar cycloaddition. The regioselective N-2 alkylation 1,4,5-trisubstituted-1,2,3-(NH)-triazoles can be made simply without regioisomers by the reaction of 4,5-disubstituted-1,2,3-(NH)-triazoles and 1-chloro-4-nitrobenzene. New ways of synthesizing regioselective 1, 4,5-trisubstituted-1,2,3-(NH)-triazoles and Sonogashira coupling in the multicomponent reaction (MRC) application are currently under investigation in our research group.

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Supporting Information Available: Experimental details and characterization data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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