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Author: Fen Zhao Zhen Chen Kai Xie Rui Yang Yu-Bo Jiang

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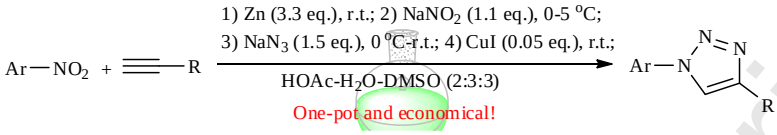
Graphical Abstract

One-pot synthesis of 1,4-disubstituted 1,2,3-triazoles from nitrobenzenes

Fen Zhao, Zhen Chen, Kai Xie, Rui Yang, Yu-Bo Jiang*

Faculty of Science, Kunming University of Science and Technology, Kunming 650500, China



A facile synthesis of 1,4-disubstituted 1,2,3-triazoles was achieved from nitrobenzenes and terminal alkynes in moderate to excellent yields under mild conditions. The reactions were successful for nitrobenzenes and terminal alkynes bearing functionalities, from which the 1,2,3-triazole derivatives were smoothly synthesized through a four-step one-pot sequence.

Original article

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Fen Zhao, Zhen Chen, Kai Xie, Rui Yang, Yu-Bo Jiang*

Faculty of Science, Kunming University of Science and Technology, Kunming 650500, China

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ABSTRACT

A facile synthesis of 1,4-disubstituted 1,2,3-triazoles was achieved from nitrobenzenes and terminal alkynes under mild conditions. The reactions were successful for nitrobenzenes and terminal alkynes bearing various functionalities, from which the 1,2,3-triazole derivatives were smoothly synthesized through a four-step one-pot sequence.

1. Introduction

1,2,3-Triazoles are an important class of heterocyclic compounds, which were widely applied in various fields including synthetic organic chemistry [1], biological science [2], medicinal chemistry [3] and material science [4]. In particular, they are found in clinical and commercial drugs such as IDO (Indoleamine 2,3-dioxygenase) inhibitors [5], antibiotics [6], HDIs (Histone deacetylase inhibitors) [7] and antiviral drugs (Fig. 1) [8].

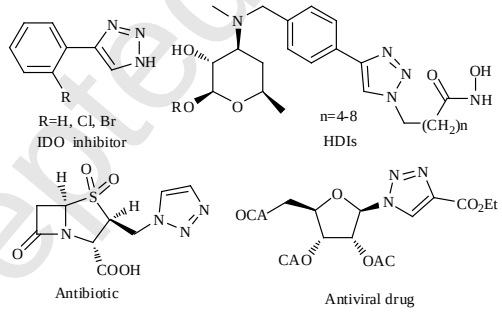
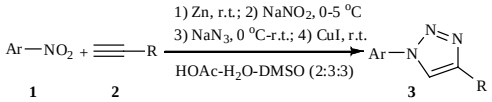


Fig. 1. Some 1,2,3-triazoles possessing pharmaceutical activities.

Because of their utility, several syntheses of 1,2,3-triazoles have been reported. The first method to form 1,2,3-triazole was the Huisgen dipolar cycloaddition, giving 1,4- and 1,5-disubstituted regioisomers [9]. In 2002, Sharpless [10] group found a copper-catalyzed 1,3-dipolar cycloaddition reaction (CuAAC) between alkynes and azides, allowing the regioselective formation of the 1,4-disubstituted 1,2,3-triazoles. From then on these compounds come to the limelight, bringing researchers to explore more effective methods using different approaches [11]. For example, the Fokin [12] group used triazole ligands TBAB to stabilize Cu (I), which can vigorously catalyze the Huisgen cycloaddition reaction to synthesize the 1,4-substituted 1,2,3-triazoles at room temperature. The Orgueira [13] group reported that the active nano-copper can also catalyze the Huisgen cycloaddition reaction. And this reaction can be carried out in various solvents such as THF, MeOH, MeCN, DMSO, DMF and so on [14]. Recently, the Ramachary [15] group reported an organocatalytic enolate-mediated synthesis of 1,2,3-triazoles from aldehydes and aryl azides, which constitutes an alternative methodology. Moreover, the synthesis of other derivatives such as 1-mono [16], 4-mono [17], 1,5-di [18], and 1,4,5-trisubsituted 1,2,3-triazoles [19] have also been reported. At the same time, some facile one-pot syntheses were demonstrated using aryldiazonium silica sulfates [20], aryl boronic acids [21], aryl halides [22] and aromatic amines [23] as the starting materials.

* Corresponding author.
E-mail address: ybjiang @ kmust.edu.cn

Based on our previous report on a one-pot synthesis of aryl azides from nitrobenzes [24], we would like to describe a convenient, efficient and economical one-pot method for the preparation of 1,4-disubstituted 1,2,3-triazoles **3** (Scheme 1), using aromatic nitrocompounds **1** and terminal alkynes **2** as the starting materials by a four-step one-pot sequence.



Scheme 1. Synthesis of 1,4-disubstituted 1,2,3-triazoles **3**

2. Experimental

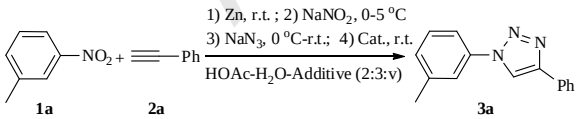
^{1}H NMR and ^{13}C NMR spectra were recorded using a MercuryPlus 300 (300 MHz) or a Bruker ACF400 spectrometer (400 MHz) in $CDCl_3$ using TMS as an internal standard. Chemical shifts for protons are reported in ppm downfield from the tetramethylsilane signal and are referenced to residual ^{1}H in the NMR solvent ($CHCl_3$: TMS). Chemical shifts for carbons are reported in ppm downfield from the tetramethylsilane signal and are referenced to the carbon resonance of the solvent ($CDCl_3$, δ 77.00). All reactions were monitored by TLC analysis using Huanghai GF254 silica gel coated plates. Column chromatography was carried out using 300–400 mesh silica gel at medium pressure. Infrared spectra were taken on a Bruker Vertex Series FTIR (KBr) and are reported in reciprocal centimeters (cm^{-1}). Melting points were obtained using a Büchi melting point apparatus and are uncorrected. HRMS spectra were recorded on Waters Micromass Premier Q-TOF spectrometer.

General procedure: A mixture of nitrobenzenes **1** (1 mmol) and Zn (215 mg, 3.3 mmol) in solvent of HOAc-H_2O (2.5 mL, v: v= 2:3) in a flask was stirred at room temperature until the starting nitrobenzenes were consumed completely (monitored by TLC analysis). $NaNO_2$ (1.1 mmol) saturated solution was added dropwise at 0-5 ^{o}C in an ice-water bath followed by adding a 1.5 mmol of NaN_3 saturated solution. Then the ice-water bath was removed and the reaction proceeded at room temperature. After 2 h, terminal alkynes **2** (1.2 mmol), CuI (0.05 mmol) and DMSO (1.5 mL) were added to the above system at room temperature. After 5 h, the mixture was treated with H_2O (15 mL) and extracted with EtOAc (3 × 15 mL) and the combined organic layer was washed with brine (3 × 5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford a crude product. Purification by column chromatography on silica gel afforded the desired 1,4-disubstitued 1,2,3-triazol **3**.

3. Results and discussion

An initial investigation of the reaction conditions was conducted using 1-methyl-3-nitrobenzene **1a** and phenylacetylene **2a** as the starting materials (Table 1). The first three steps of the reaction (including reduction, diazotization, and azidization) can go smoothly in the solvent of a HOAc-H_2O-additive mixture (2:3:x, v/v), but no target molecule of 4-phenyl-1-(*m*-tolyl)-1*H*-1,2,3-triazole **3a** was detected when no additive solvent was present (Table 1, entry 1). When additive solvents such as MeOH, $CHCl_3$, THF, DCM and EtOH were used, the product can be obtained although the yields were low (Table 1, entries 2-8). And higher yields of 43% and 60% were obtained respectively when 3 portions (in volume) of DMF or DMSO were used as the additive solvent (Table 1, entries 9, 14), while only lower yields can be obtained when more or less amount of additive solvent was used (Table 1, entries 9-15). The effect of the amount of catalyst was also tested (Table 1, entries 17, 18), and an improved yield of **3a** was obtained when 0.05 equiv. of CuI was added using DMSO as an additive (Table 1, entry 17). However, only 30% yield was obtained when 0.02 equiv of CuI was added (Table 1, entry 18). To our delight, the yields can be increased if the additive solvent was added in the last step (Table 1, entry 9 *vs.* 12, 14 *vs.* 16). Additionally, we examined some other copper catalysts such as CuBr, CuO, CuCl and $Cu(OAc)_2$, finding they were less efficient for this system (Table 1, entries 20-23). As a result, the optimal conditions appeared 0.05 equiv. of CuI using HOAc-H_2O-DMSO (2:3:3, v/v) as the solvent, with DMSO being added in the last step (Table 1, entry 19).

Table 1
Optimization of the reaction conditions.[a]



Entry	Catalyst (equiv.)	Additive (x)	Yield (%)[b]
1	CuI (0.1)	----	0
2	CuI (0.1)	MeOH (3)	21
3	CuI (0.1)	^{t}BuOH (3)	24
4	CuI (0.1)	95% EtOH (3)	25
5	CuI (0.1)	EtOH (3)	27
6	CuI (0.1)	DCM (3)	28
7	CuI (0.1)	CHCl3 (3)	26
8	CuI (0.1)	THF (3)	30
9	CuI (0.1)	DMF (3)	43

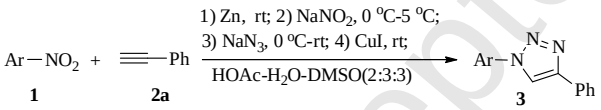
10	CuI (0.1)	DMF (2)	21
11	CuI (0.1)	DMF (4)	20
12	CuI (0.1)	DMF (3)	54[c]
13	CuI (0.1)	DMSO (2)	38
14	CuI (0.1)	DMSO (3)	60
15	CuI (0.1)	DMSO (4)	35
16	CuI (0.1)	DMSO (3)	70[c]
17	CuI (0.05)	DMSO (3)	65
18	CuI (0.02)	DMSO (3)	30
19	CuI (0.05)	DMSO (3)	84[c]
20	CuBr (0.05)	DMSO (3)	38[c]
21	CuO (0.05)	DMSO (3)	30[c]
22	CuCl (0.05)	DMSO (3)	32[c]
23	$Cu(OAc)_2$ (0.05)	DMSO (3)	35[c]

[a] Reaction conditions: **1a** (1 mmol), Zn (3.3 mmol), HOAc (1 mL), H_2O (1.5 mL), $NaNO_2$ (1.1 mmol), NaN_3 (1.5 mmol), phenylacetylene **2a** (1.2 mmol), and catalyst.
[b] Yield of isolated product after column chromatography.
[c] Additive solvent was added in the last step.

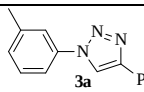
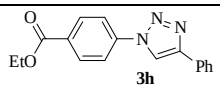
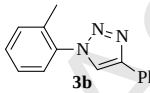
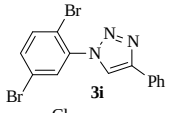
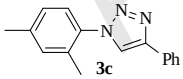
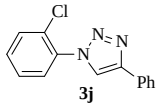
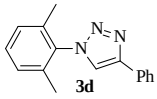
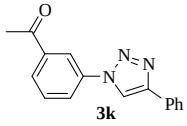
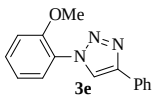
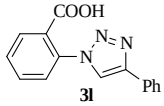
With the optimized reaction conditions in hand, a series of nitrobenzenes **1** and phenylacetylene **2a** were then subjected to the reaction, affording the corresponding 1,4-disubstituted 1,2,3-triazoles **3**. The results summarized in Table 2 showed that nitrobenzenes carrying either an electron donating substituent such as methyl, methoxy and amido group (Table 2, entries 1-7) or an electron withdrawing group including halogen, alkoxycarbonyl, carbonyl and carboxyl (Table 2, entries 8-13) could proceed successfully. Substrates bearing an electron- donating group at the *para*- or *ortho*-position of the nitrobenzenes could all give the corresponding 1,2,3-triazoles in good to excellent yields (Table 2, entries 5, 6). Additionally, the functional groups in the nitrobenzenes such as carbonyl, alkoxycarbonyl, and carboxyl were tolerated under the conditions (Table 2, entries 11-13). However, the yields were somehow lower when the substituents contain Cl or Br (Table 2, entries 9, 10).

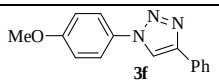
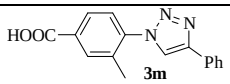
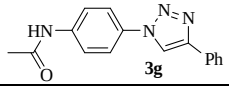
We also examined the scope of terminal alkynes, as summarized in Table 3. 1-Methyl-2-nitrobenzene **1b** and terminal alkynes **2** were allowed to react in one pot under the optimal conditions to give the desired 1,4-disubstitued 1,2,3-triazols. To our delight, various substituted terminal alkynes, regardless of the substitution patterns (with electron-withdrawing or donating groups), affording the desired products in moderate to high yields (Table 3, entries 1-13). It is noteworthy that heterocycles such as ethynylpyridine and ethynyl thiophene were also tolerated as substrates to afford the desired products in high yields (Table 3, entries 10-13). Additionally, the reaction of terminal alkynes carrying electron-donating and electron-withdrawing group (Cl, Br) at the *para*-position could also furnish the 1,2,3-triazoles in high yields (Table 3, entries 8, 9). Alkyl terminal alkynes can also be employed in this system, providing the desired products in excellent yields (Table 3, entries 3, 4).

Table 2
Synthesis of 1,4-disubstituted 1,2,3-triazoles **3** by expanding aromatic nitrocompounds.[a]



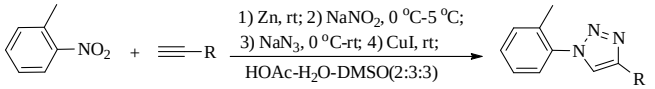
1 **2a** **3**

Entry	Product	Yield (%)[b]	Entry	Product	Yield (%)[b]
1	 **3a**	84	8	 **3h**	85
2	 **3b**	91	9	 **3i**	24
3	 **3c**	97	10	 **3j**	27
4	 **3d**	95	11	 **3k**	65
5	 **3e**	80	12	 **3l**	58

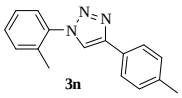
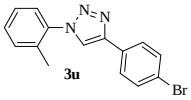
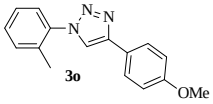
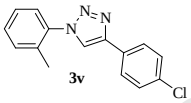
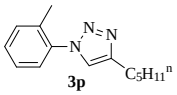
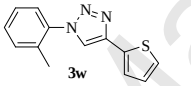
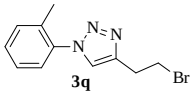
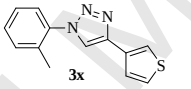
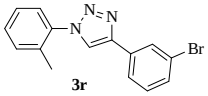
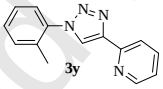
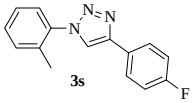
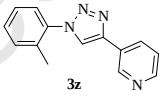
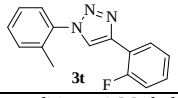
6	 **3f**	76	13	 **3m**	95
7	 **3g**	73			

[a] Reaction conditions: nitrobenzenes **1** (1 mmol), Zn (3.3 mmol), 2.5 mL HOAc-H_2O (2:3), 1.1 mmol of $NaNO_2$, 1.5 mmol NaN_3, phenylacetylene **2a** (1.2 mmol), CuI (0.05 mmol), and DMSO (1.5 mL).
[b] Yield of isolated product after column chromatography.

Table 3
Synthesis of 1,4-disubstituted 1,2,3-triazoles **3** by expanding terminal alkynes.[a]



1b **2** **3**

Entry	Product	Yield (%)[b]	Entry	Product	Yield (%)[b]
1	 **3n**	95	8	 **3u**	79
2	 **3o**	84	9	 **3v**	90
3	 **3p**	90	10	 **3w**	90
4	 **3q**	88	11	 **3x**	92
5	 **3r**	60	12	 **3y**	83
6	 **3s**	64	13	 **3z**	93
7	 **3t**	60			

[a] Reaction conditions: 1-Methyl-2-nitrobenzene **1** (1 mmol), Zn (3.3 mmol), 2.5 mL HOAc-H_2O (2:3), 1.1 mmol $NaNO_2$,1.5 mmol NaN_3, terminal alkyne **2** (1.2 mmol), CuI (0.05 mmol), and DMSO (1.5 mL).
[b] Yield of isolated product after column chromatography.

4. Conclusion

In summary, we have developed a highly efficient protocol for the synthesis of 1,4-disubstitued 1,2,3-triazoles using nitrobenzenes and terminal alkynes as the starting materials, in which a four-step one-pot sequence was involved under mild conditions. It is an economical and facile method for the preparation of 1,2,3-triazole derivatives, which are widely applied in many fields.

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