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Original article

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

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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].

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.

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.

## 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 ($CDCl_3$, $\delta$ 77.00). All reactions were monitored by TLC analysis using Huanghai

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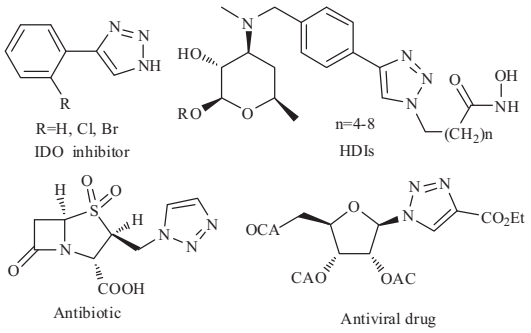
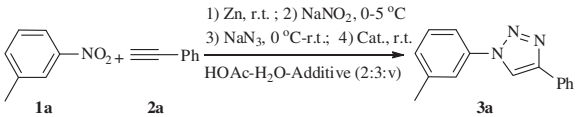



**Fig. 1.** Some 1,2,3-triazoles possessing pharmaceutical activities.

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 °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**.

**Table 1**
Optimization of the reaction conditions.[a]



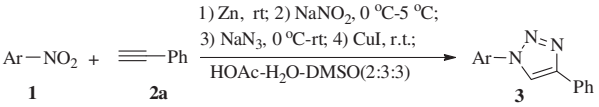

| Entry | Catalyst (equiv.) | Additive (x) | Yield (%)[b] |
|---|---|---|---|
| 1 | CuI (0.1) | – | 0 |
| 2 | CuI (0.1) | MeOH (3) | 21 |
| 3 | CuI (0.1) | $^t$BuOH (3) | 24 |
| 4 | CuI (0.1) | 95% EtOH (3) | 25 |
| 5 | CuI (0.1) | EtOH (3) | 27 |
| 6 | CuI (0.1) | DCM (3) | 28 |
| 7 | CuI (0.1) | CHCl3 (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] |

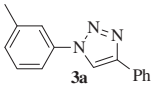
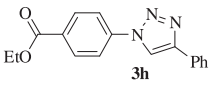
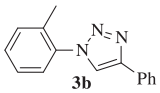
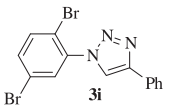
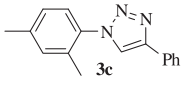
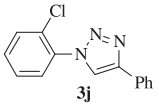
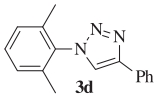
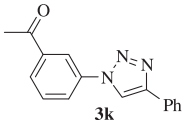
[a] Reaction conditions: **1a** (1 mmol), Zn (3.3 mmol), HOAc (1 mL), $H_2O$ (1.5 mL), $NaNO_2$ (1.1 mmol), $NaN_3$ (1.5 mmol), phenylacetylene **2a** (1.2 mmol), and catalyst.
[b] Yield of isolated product after column chromatography.
[c] Additive solvent was added in the last step.

## 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

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




| 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 |