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## Simple synthesis of 1-substituted-4-vinyl-1,2,3-triazoles based on polystyrene-supported sulfonyl chloride

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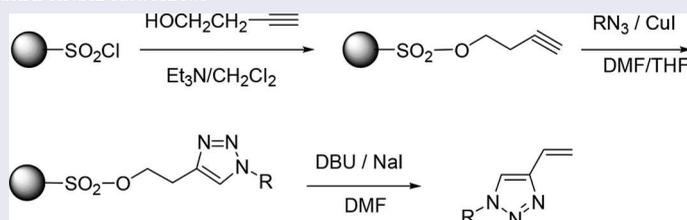
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### ABSTRACT

Polystyrene-supported but-3-ynyl sulfonate reagent has been developed and applied to the traceless solid-phase organic synthesis of 1-substituted-4-vinyl-1,2,3-triazoles by CuI-promoted 1,3-dipolar cycloaddition reaction with various organic azides and subsequent cleavage from the polymer support through elimination reaction mediated by 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU). The advantages of this new synthetic method include simple operation and moderate to good yields of the products, as well as good stability of the reagent.

### GRAPHICAL ABSTRACT



### ARTICLE HISTORY

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### KEYWORDS

Click chemistry; elimination reaction; solid-phase organic synthesis; polystyrene-supported but-3-ynyl sulfonate; 4-vinyl-1,2,3-triazoles

## Introduction

1,2,3-Triazoles are an important class of nitrogen-containing heterocycles<sup>[1]</sup> and have displayed an ample range of applications in synthetic, pharmaceutical, agrochemical, medicinal, and material chemistry.<sup>[2]</sup> Since Sharpless's<sup>[3]</sup> and Meldel's<sup>[4]</sup> groups developed the copper-catalyzed Huisgen's 1,3-dipolar cycloaddition (CuAAC) reaction between azides and terminal alkynes, "click chemistry" has received growing interest in the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles. So far, many synthetic methods for achieving this ring system have been developed for different purposes.<sup>[5]</sup> Among them, vinyl-substituted 1,2,3-triazoles are useful vinyl monomers and have been demonstrated to take advantage of the 1,2,3-triazole subunit and combine the features found in classical monomers, such as aromaticity, polarity, and structural diversity inherent in styrenics, vinylpyridines, and acrylates, respectively, into a single building block.<sup>[6]</sup> Despite their

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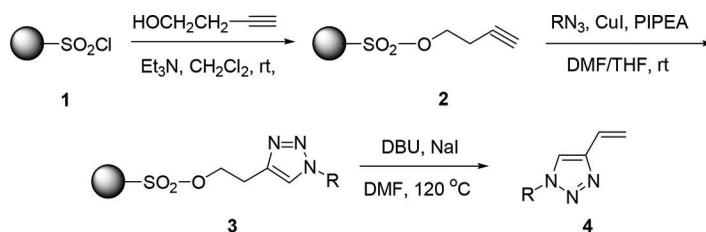
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importance, there are relatively few reports on their preparation.<sup>[7]</sup> Moreover, up to now, only several typical vinyl-substituted 1,2,3-triazoles such as 1-benzyl-4-vinyl-1*H*-1,2,3-triazole,<sup>[8a]</sup> 1-vinyl-5,6-dihydro[1,2,3]triazolo[5,1-*a*]isoquinoline,<sup>[8b]</sup> 5-vinyl-1*H*-1,2,3-triazoles,<sup>[8c]</sup> and 4-phenyl-1-(1-phenylvinyl)-1*H*-1,2,3-triazole<sup>[8d]</sup> have been described. Therefore, development of new methodologies for the facile synthesis of functionalized vinyl-substituted 1,2,3-triazoles is highly desirable. In our previous work, we reported an efficient solid-phase organic synthesis (SPOS) protocol for the preparation of 1-vinyl-1,2,3-triazoles via a versatile traceless selenium linker.<sup>[9]</sup> Based on our previous work and by taking advantage of SPOS (such as driving the reaction to completion by the use of excess reagents, removing excess or consumed reagents by a simple filtration workup operation, and isolating products easily by filtration from the solid support),<sup>[10]</sup> we report in this work an efficient SPOS method for 1-substituted-4-vinyl-1,2,3-triazoles based on polystyrene-supported but-3-ynyl sulfonate reagent, as outlined in Scheme 1. To the best of our knowledge, SPOS of 4-vinyl-1,2,3-triazoles has not been investigated. Compared with polymer-supported selenium reagent,<sup>[9]</sup> the present polystyrene-supported sulfonate reagent is easy to prepare. Moreover, this method provides a convenient access to introduce vinyl into the 4-position of the 1,2,3-triazole rings, which is usually difficult to achieve.

Initially, polystyrene-supported sulfonyl chloride **1** was conveniently prepared from a commercially available 2% cross-linked benzenesulfonic acid resin by treating it with thionyl chloride in *N,N*-dimethylformamide according to a previous reported procedure.<sup>[11]</sup> In the presence of triethylamine, 3-butyn-1-ol was reacted with sulfonyl chloride resin **1** at room temperature almost quantitatively to afford but-3-ynyl sulfonate resin **2** (no chlorine was found by microanalysis of resin **2** and its loading was estimated gravimetrically to be 3.52 mmol/g), which were monitored by Fourier transfer (FTIR), exhibiting the infrared absorption band at 1365 cm<sup>-1</sup> (-S-O stretch of -SO<sub>2</sub>Cl for resin **1**), which shifted to 1352 cm<sup>-1</sup> (-SO<sub>2</sub>-O-), and appearing a characteristic absorption peak of carbon-carbon triple bond absorption at 2120 cm<sup>-1</sup>.

Next, the 1,3-dipolar cycloaddition reaction of resin **2** with various azides, the key for the success of this protocol was then investigated. Different catalysts have been reported to promote the CuAAC reaction. Among them, copper(I) salts can be used directly or generated in situ by reduction of Cu(II) salts with reducing agents to catalyzed this process smoothly for the preparation of 1,4-disubstituted-1*H*-1,2,3-triazoles exclusively.<sup>[3-5]</sup> By this way, the CuAAC reaction can be smoothly performed under milder conditions avoiding the use of an inert atmospheres. Based on these studies and inspired by our previous work on the SPOS of 1-vinyl-1,2,3-triazoles, benzyl azide was chosen here for the template reaction with resin **2**, and reaction conditions such as several solvents including tetrahydrofuran (THF), dimethylfuran (DMF), dimethylsulfoxide (DMSO), and CH<sub>2</sub>Cl<sub>2</sub>, and their combinations in



**Scheme 1.** Solid-phase synthetic route to 1-substituted-4-vinyl-1,2,3-triazoles.

the presence of copper(I) catalysts like CuI, CuCl, CuBr, and CuSO<sub>4</sub>/sodium ascorbate, amounts of catalyst, and reaction time were evaluated. After this, the 1,3-dipolar cycloaddition of resin **2** with benzyl azide proceeded smoothly in DMF/THF in the presence of diisopropylethyl amine (DIPEA) and catalytic amounts of CuI at room temperature for 12 h to afford the 2-(4-triazolyl)ethyl sulfonate resin (**3a**), which can also be monitored by the IR spectrum conveniently and precisely in which the characteristic signal of the carbon-carbon triple bond absorption (2120 cm<sup>-1</sup>) has been distinctly shrunk after 6 h of reaction time, and then disappeared completely for another 10 h of reaction time.

Finally, the cleavage conditions with different bases [triethylamine, pyridine, 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU), and potassium carbonate], various solvents (MeCN, DMF, THF, 1,4-dioxane), as well as different reaction temperatures and times were examined, and the optimal result was obtained by treating resin **3a** in DMF with DBU in the presence of NaI at 120 °C for 1 h, resulting in the exclusive formation of 1-benzyl-4-vinyl-1*H*-1,2,3-triazole (**4a**) in 90% total yield based on the loading of resin **2** (entry 1, Table 1). The <sup>1</sup>H NMR spectrum of **4a** displayed a distinct singlet at δ = 7.45 ppm for the triazolyl C<sub>5</sub>-H proton, a singlet signal for the *N*-CH<sub>2</sub> protons appearing at δ = 5.49 ppm. The signals of the vinyl protons as a double doublet were also observed at δ = 6.65 (dd, *J* = 17.8, 11.2 Hz), 5.85 (d, *J* = 17.8 Hz), and 5.30 ppm (d, *J* = 11.2 Hz), respectively. In addition, the melting point of this compound is in agreement with the reported value.<sup>[8a]</sup>

With the optimized conditions (CuAAC reaction and base-catalyzed elimination) in hand, the generality of the method was further evaluated using a variety of azides and the resin **2**, and the corresponding target compounds 4-vinyl-1,2,3-triazoles (**4a–4m**) were obtained. As observed in Table 1, a range of benzylic azides (entries 1–3, Table 1) and primary azides (entries 4–6, Table 1) were found to react readily to form the desired triazole products in good yields (80–90%). Of the azides investigated in this study, aryl azides carrying either an electron-donating substituent (entries 8–10, Table 1) or an electron-withdrawing group (entries 11–13, Table 1) could also perform efficiently with moderate to excellent yields. Furthermore, greater yields were obtained when the substrates had an electron-donating or electron-withdrawing substituent both at *meta*- and *para*-positions. However, the more sterically hindered aryl azides bearing an *ortho*-group (entries 10 and 11, Table 1) afforded the products in lower yields.

**Table 1.** Yields of 4-vinyl-1,2,3-triazoles (**4a–4m**).

Entry	R	Product	Yield <sup>a</sup> (%)
1	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	<b>4a</b>	90
2	4-MeOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	<b>4b</b>	86
3	4-BrC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	<b>4c</b>	83
4	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub>	<b>4d</b>	84
5	HOCH <sub>2</sub> CH <sub>2</sub>	<b>4e</b>	80
6	CH <sub>3</sub> OCOCH <sub>2</sub> CH <sub>2</sub>	<b>4f</b>	81
7	C <sub>6</sub> H <sub>5</sub>	<b>4g</b>	90
8	4-MeOC <sub>6</sub> H <sub>4</sub>	<b>4h</b>	92
9	3-MeC <sub>6</sub> H <sub>4</sub>	<b>4i</b>	91
10	2-MeC <sub>6</sub> H <sub>4</sub>	<b>4j</b>	65
11	2-ClC <sub>6</sub> H <sub>4</sub>	<b>4k</b>	62
12	4-BrC <sub>6</sub> H <sub>4</sub>	<b>4l</b>	89
13	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>4m</b>	88

<sup>a</sup>Isolated total yields were based on the loading of the resin **2**.

In conclusion, we have developed a facile method for the traceless solid-phase synthesis of 1-substituted-4-vinyl-1*H*-1,2,3-triazoles by CuI-catalyzed 1,3-dipolar cycloaddition reaction of polymer-bound but-3-ynyl sulfonate with organic azides such as benzylic azides, primary azides, and aryl azides and subsequent DBU-promoted elimination reaction. This method provides novel access to 4-vinyl-1*H*-1,2,3-triazoles in moderate to excellent yields with simplification of product workup.

## Experimental

Melting points Are uncorrected.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker Avance (400-MHz) spectrometer, using  $\text{CDCl}_3$  as the solvent and TMS as internal reference. IR spectra were taken on a Perkin-Elmer SP One FTIR spectrophotometer. Microanalyses were performed with a Carlo Erba 1106 Elemental Analyzer, and 2% cross-linked benzene-sulfonic acid resin (4.5 mequiv/g) was used for the preparation of sulfonyl chloride resin **1** (loading = 4.1 mmol Cl/g) according to the reported method.<sup>[11]</sup> All organic azides are known compounds and were prepared by reaction of  $\text{NaN}_3$  with organic halides in DMF according the literature procedure.<sup>[12]</sup> The other starting materials were purchased from commercial sources and used without further purification. THF was newly distilled from sodium benzophenone immediately before use. DMF was purified by distillation under reduced pressure over calcium hydride prior to use.

### *Procedure for the preparation of resin 2*

Under a nitrogen atmosphere, 3-butyn-1-ol (8.0 mmol) and triethylamine (1.1 mL, 8.0 mmol) were added to sulfonyl chloride resin **1** (0.50 g, 2.0 mmol) preswollen in  $\text{CH}_2\text{Cl}_2$  (10 mL) for 1 h, and the resulting mixture was stirred overnight at room temperature. After this, the resin **2** was collected by filtration and washed successively with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 10$  mL),  $\text{H}_2\text{O}$  ( $2 \times 10$  mL), MeOH ( $2 \times 10$  mL), and  $\text{CH}_2\text{Cl}_2$  ( $2 \times 10$  mL) and then dried in vacuo to give **2** as a pale-yellow resin. The loading in resin **2** was determined gravimetrically to be 3.52 mmol/g. IR (KBr):  $\nu = 3305, 2962, 2120, 1600, 1491, 1352, 1300, 1131, 1050, 961, 820, 749 \text{ cm}^{-1}$ .

### *General procedure for the preparation of 4-vinyl-1,2,3-triazoles*

Resin **2** (0.57 g, 2.0 mmol) was swelled in THF/DMF (15 mL, 2:1) at room temperature for 30 min under nitrogen. Then azide (8.0 mmol), CuI (19.0 mg, 0.1 mmol), and DIPEA (1.0 mL, 7.7 mmol) were added, and the mixture was stirred at room temperature. This progression of the reaction was monitored by IR spectroscopy. After disappearance of the signal near  $2100 \text{ cm}^{-1}$ , the suspension was filtered through the vessel frit and the resin was washed successively with  $\text{H}_2\text{O}$  ( $2 \times 10$  mL), DMF ( $2 \times 10$  mL), MeOH ( $2 \times 10$  mL), and  $\text{CH}_2\text{Cl}_2$  ( $2 \times 10$  mL) and dried in vacuo to give resin **3**. The resin **3** was then swelled in DMF (15 mL) for 30 min under a nitrogen atmosphere. NaI (0.9 g, 0.6 mmol) and DBU (0.6 g, 4.0 mmol) were added this suspension mixture, which was heated to  $120^\circ\text{C}$  and kept at this temperature for 1 h. Upon completion, the mixture was cooled and the resin was collected by filtration and washed with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 10$  mL). The filtrate was washed with water ( $2 \times 30$  mL), dried over magnesium sulfate, and concentrated to afford crude products

**4a–4 m**, which were further purified via flash column chromatography (hexane–EtOAc, 10:1) for their structural analysis.

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