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Cu(I)-promoted one-pot "Click-S_NAr reaction" of nitrobenzaldehydes

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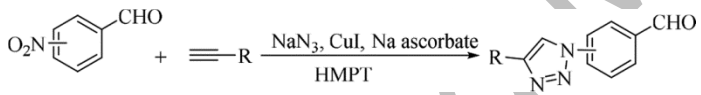
Abstract

A series of 1,4-disubstituted 1,2,3-triazoles containing formyl was synthesized from a variety of readily available nitrobenzaldehydes and alkynes via a convenient one-pot "click-S_NAr reaction" with moderate to excellent yields. The reactions were easily carried out in hexamethyl phosphoramide in the absence of a base at 60 °C.

GRAPHICAL ABSTRACT



KEYWORDS: Click chemistry, 1,2,3-Triazoles, Heterocycle, Copper catalysis

INTRODUCTION

The 1,2,3-triazole ring is an important structure in the pharmaceutical and agrochemical industries [1]. The discovery of the Cu (I)-catalyzed 1,3-dipolar cycloaddition of azides and terminal alkynes has further triggered the conduct of studies on both the structure and synthesis of this heterocycle [2]. The widely used Cu (I)-catalyzed method offers many advantages, such as exclusive regioselectivity, wide substrate scope, mild reaction

conditions, and excellent yields. Moreover, the formed molecules containing the 1,2,3-triazole structure are widely found in biological activities, including antibacterial [3], herbicidal, antifungicidal [4], antiallergic [5], and anti-HIV activities [6], and they serve as selective b3 adrenergic receptor agonists [7–9].

The rapidly increasing need for these hetero-compounds has prompted researchers to develop effective methods for preparing diverse 1,2,3-triazole derivatives. In our previous work, we reported several 4(3H)-quinazolinones containing 1,2,3-triazole moiety conjugated with Schiff base, in which 1,2,3-triazoles containing formyl were obtained in a two-step process given that the azido benzaldehyde had to be isolated separately [10–12]. Other groups have also reported on the synthesis of 1,4-disubstituted 1,2,3-triazoles from terminal alkynes [13]. Multicomponent reactions have offered a rapid and efficient route to generate complex molecular frameworks from simple and rapidly available substrates owing to their excellent catalytic efficiency in most cases [14]. In the present study, we proposed a novel method for preparing a series of 1,2,3-triazoles containing formyl from nitrobenzaldehydes, sodium azide, and alkynes by using a one-pot "click-S_NAr reaction" (Figure 1).

RESULTS AND DISCUSSION

The optimum reaction conditions were preliminarily screened using *p*-nitrobenzaldehyde **1a** (1 mmol), NaN_3 (1.2 equiv.), and alkyne **2a** (1.1 equiv.) as model substrates (Table 1). We initially investigated the effects of various solvents on the formation of triazole **3a**. Hexamethyl phosphoramide (HMPT) was considerably more effective than the other solvents and showed an excellent yield of 89% at 60 °C within 2 h (Table 1, entry 7). No product was obtained when water was used as solvent probably because of the low solubility of some of the starting materials (entry 5). By contrast, the reactions using DMSO or DMF as solvent generated products in moderate yields (entries 1–2). *N*-methyl-2-pyrrolidone (NMP) as solvent was apparently suitable for the system because of its good yield of 85% at 60 °C for 24 h (entry 6). The effects of various amounts of CuI and sodium ascorbate were also investigated (Table 1, entries 9–11). As expected, 0.2 equiv. of CuI and 0.4 equiv. of sodium ascorbate were necessary in the cycloaddition. Thus, the reaction should be catalyzed by copper (I) iodide (0.2 equiv.) and sodium ascorbate (0.4 equiv.) in HMPT at 60 °C for 2 h or at room temperature for 24 h.

The substrates scope of this one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles catalyzed by the copper (I) catalyst was investigated under optimized conditions, and the results are summarized in Table 2. This protocol is apparently applicable to alkynes carrying either an aryl group, including electron donating substituents (e.g., ethyl and alkoxy, entries 3–4) and electron withdrawing substituents (e.g., chloro, fluoro, entries 5–6), or an aliphatic group, such as chloromethyl, hydroxymethyl, *n*-amyl, and carboxyl (entries 8–11); this method showed moderate to excellent yields. The electronic effects

and the positions of the substituents did not appreciably influence the reaction. Unlike the *p*-substituents, the substrates bearing an *o*-substituent suffer from a low reaction rate with a low yield at 80 °C within 4 h (entry 13) probably because of the steric hindrance effect, as well as the occurrence of the by-product benzoxazole, which was reported by Stokes et al [15]. However, a decarboxylation product **3l** was unexpectedly observed when we used propiolic acid as substrate under the same conditions. To further investigate, we changed the temperature from 60 °C to 25 °C for 12 h. The adduct **3k** containing a carboxylic substituent was obtained at a yield of 79%. In addition, the decarboxylation product **3m** was observed when we reacted *o*-nitrobenzaldehyde instead of *p*-nitrobenzaldehyde with propiolic acid at 80 °C for 4 h. The decarboxylation product was previously reported by Kuang et al. [16]. When propiolic acid was used as substrate in the presence of DBU, the reactions produced a decarboxylation product at 130 °C and a product containing a carboxylic substituent at temperatures below 25 °C.

EXPERIMENTAL

Melting points were recorded on a Fischer–Johns micro hot-stage apparatus and were uncorrected. IR spectra were recorded on a Nexus FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV400 MHz spectrometer by using tetramethylsilane as internal standard and DMSO-d_6 or $CDCl_3$ as solvent at room temperature. Elemental analyses were performed using a Perkin–Elmer 2400 CHNS elemental analyzer. Mass spectra were obtained using a Finnigan MAT-95 mass spectrometer. All reactions were monitored by TLC equipped with Huanghai GF 254

silica gel-coated plates. Column chromatography was performed using 100–200 mesh silica gel under medium pressure. All the reagents for the synthesis were commercially available and used as received or purified via standard methods prior to use.

General Procedure for the Synthesis of 1,2,3-triazoles (3a-m)

The solution of *o*- or *p*-nitrobenzaldehyde (151 mg, 1 mmol), NaN_3 (78 mg, 1.2 mmol), alkyne (1.1 mmol), CuI (38 mg, 0.2 mmol), and Na ascorbate (79 mg, 0.4 mmol) in HMPT (3 mL) in a round-bottom flask was stirred under N_2. The mixture was heated to the temperature indicated in Table 2 until the starting *o/p*-nitrobenzaldehyde was completely consumed (monitored by TLC). The mixture was diluted with H_2O and then extracted with EtOAc or CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with sat. brine (3 × 30 mL), dried with anhyd. Na_2SO_4, and concentrated under reduced pressure to obtain the crude product, which was purified via flash chromatography (silica gel, particle size 100–200 mesh, *n*-hexane-EtOAc) or crystallized by EtOAc.

Spectral Characterization of 3c

Compound 4-(4-(4-ethylphenyl)-1H-1,2,3-triazol-1-yl)benzaldehyde (**3c**) was obtained as white solid. Yield: 92%, mp: 193.5 °C–196.0 °C. IR (KBr): 3137, 2961, 1691, 1604, 1591, 1411, 1230 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 10.10 (s, 1H), 8.27 (s, 1H), 8.10 (d, J = 8.6 Hz, 2H), 8.04 (d, J = 8.6 Hz, 2H), 7.85 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 2.72 (q, J = 7.6 Hz, 2H), 1.30 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.66, 149.08, 145.14, 141.06, 135.94, 131.40, 128.54, 127.13, 125.96, 120.38, 116.84,

28.74, 15.49. MS (ESI): *m/z* 278 $(M+H)^+$. Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.59; H, 5.46; N, 15.19.

CONCLUSIONS

A simple and efficient method used to directly prepare 1,4-disubstituted 1,2,3-triazoles containing formyl from a variety of aromatic and aliphatic alkynes, sodium azide, and *o*- and *p*-nitrobenzaldehyde was developed. This method displayed moderate to excellent yields. Further studies on the applications of the proposed methodology to the synthesis of biologically active compounds are ongoing.

ACKNOWLEDGMENT

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SUPPLEMENTARY MATERIAL

Complete experimental details and the ^1H and ^{13}C NMR spectra obtained in this study can be found in the "Supplementary Content" section of this article's webpage.

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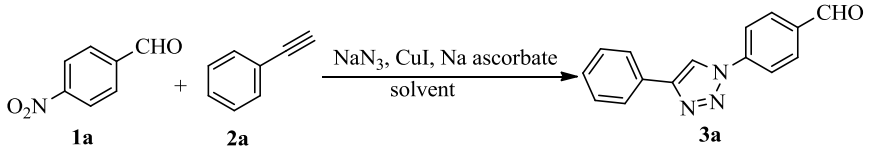
Table 1. Optimization of the Synthesis of

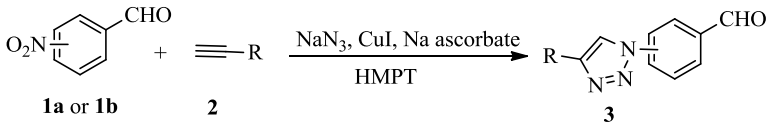
4-(4-phenyl-1H-1,2,3-triazol-1-yl)benzaldehyde (**3a**) [a]



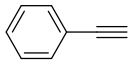
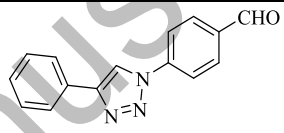
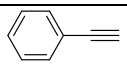
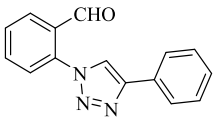
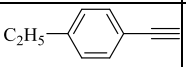
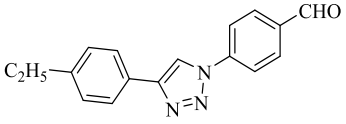
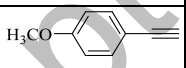
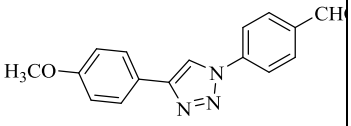
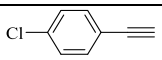
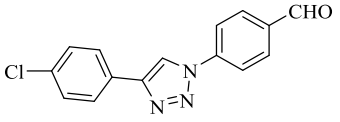
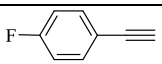
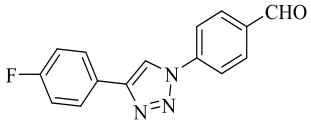
Entry	CuI (equiv.)	Sodium ascorbate (equiv.)	Solvent	Temperature (°C)	Time (h)	Yield [a] of 3a (%)
1	0.2	0.4	DMSO	60	24	45
2	0.2	0.4	DMF	60	24	16
3	0.2	0.4	MeCN	60	24	10
4	0.2	0.4	Dioxane	60	24	7
5	0.2	0.4	H_2O	60	24	0
6	0.2	0.4	NMP	60	24	80
7	0.2	0.4	HMPT	60	2	90
8	0.2	0.4	HMPT-H_2O (9:1)	60	2	75
9	0.2	0.4	HMPT	25	24	83
10	0.5	1	HMPT	60	2	91
11	0.1	0.2	HMPT	60	2	73

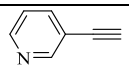
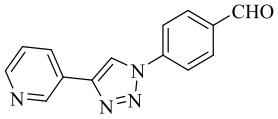
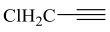
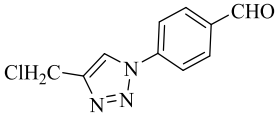
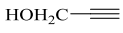
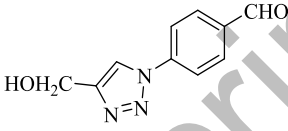
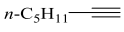
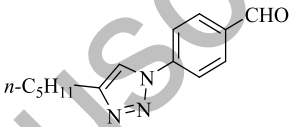
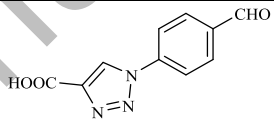
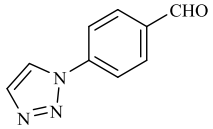
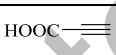
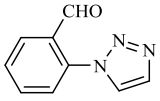
[a] Yield of isolated product from reaction on a 1 mmol scale.

Table 2. Preparation of 1,2,3-triazoles containing formyl (**3**) [a]



1a or **1b** **2** **3**

Entry	Aldehyde **1**	Alkynes **2**	T (°C)	Time (h)	Product **3**		Yield [b] of 3 (%)
1	**1a**		60	2	**3a**		90
2	**1b**		80	4	**3b**		68
3	**1a**		60	2	**3c**		92
4	**1a**		60	2	**3d**		87
5	**1a**		60	2	**3e**		86
6	**1a**		60	2	**3f**		90

7	**1a**		60	2	**3g**		83
8	**1a**		60	2	**3h**		89
9	**1a**		60	2	**3i**		87
10	**1a**		60	2	**3j**		92
11	**1a**		25	12	**3k**		79
12	**1a**		60	2	**3l**		86
13	**1b**		80	4	**3m**		73

[a] Reaction conditions: **1** (1 mmol), NaN_3 (1.2 mmol), alkyne (1.1 mmol), CuI (0.2 equiv.), and sodium ascorbate (0.4 equiv.) in HMPT (3 mL); [b] Isolated yields.

Figure 1. One-pot click-S_NAr reaction used to prepare 1,2,3-triazoles containing formyl