Cu(I)-promoted One-pot Synthesis of 1,4-Disubstituted 1,2,3-Triazoles from anti-3-Aryl-2,3-dibromopropanoic Acids and Nitrobenzaldehydes

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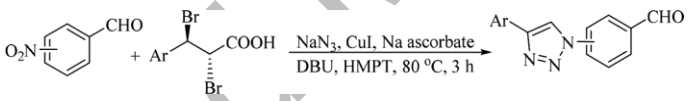
Abstract

A series of 1,4-disubstituted 1,2,3-triazoles were synthesized through a one-pot process from easily available *anti*-3-aryl-2,3-dibromopropanoic acids and nitrobenzaldehydes in hexamethylphosphoric triamide (HMPT). Inexpensive copper(I) iodide was the catalyst.

GRAPHICAL ABSTRACT



KEYWORDS: 1,2,3-triazoles, *anti*-3-aryl-2, 3-dibromopropanoic acid, click chemistry, one-pot

INTRODUCTION

1,2,3-Triazoles have been intensively studied in recent years because of their widespread applications in pharmaceuticals and agrochemicals.[1] In many cases, these compounds have exhibited interesting biological activities, including antibacterial,[2] antifungicidal,[3] antiallergic,[4] and anti-HIV activities.[5]

The discovery of Cu(I)-catalyzed 1,3-dipolar cycloaddition of azides and terminal alkynes has further stimulated the research on both the structure types and preparation methods of these heterocycles.[6] This vigorous "click chemistry" [3+2]-cycloaddition reactions have been very attractive and extensively used in the preparation of diverse 1,4-substituted 1,2,3-triazoles[7] due to its several advantages, such as exclusive regioselectivity, wide substrate scope, mild reaction conditions, and excellent yields. However, the method also has a limitation in that the starting materials of terminal alkynes and organic azides need to be prepared and isolated respectively ahead, which restricts its applications in wide fields. Hence, explorations for new methods that do not employ the terminal alkynes and azides are much desired. In our previous works, we have reported some interesting one-pot syntheses of various 1,2,3-triazole derivatives from easily available *anti*-3-aryl-2,3-dibromopropanoic acids.[8] As a part of our continuing interests in one-pot "click chemistry", we herein report our results on the one-pot synthesis of 1, 4-disubstituted 1,2,3-triazoles containing formyl group from easily available nitrobenzaldehydes and *anti*-3-aryl-2,3-dibromopropanoic acids. In these reactions, the *anti*-3-aryl-2, 3-dibromopropanoic acids served as terminal alkyne precursors and nitrobenzaldehydes served as organic azides precursors. The direct use of terminal alkynes and organic azides was not needed (Scheme 1).

RESULTS AND DISCUSSION

To identify the optimal reaction conditions, we used nitrobenzaldehyde **1a** and *anti*-3-phenyl-2,3-dibromopropanoic acid **2a** as model substrates (Table 1). Initially, we chose the inorganic compounds of potassium carbonate and cesium carbonate, respectively, as the base for the solvent of hexamethylphosphoric triamide (HMPT). The reaction was performed for 24 h at 80 °C with a catalyst system consisting of copper(I) iodide (0.2 equiv.) and sodium ascorbate (0.4 equiv.). The moderate yield products were isolated (Table1, entry 1–2). We then examined some organic bases and found out that no target molecules were detected when triethylamine was used (Table1, entry 3). To our interest, a yield of 88% was obtained when 1,8-diazabicuclo[5.4.0]undeo-7-ene (DBU) was applied at 80 °C for 3 h (Table1, entry 4). With this result, we then investigated the effect of the solvents, such as DMSO, DMF, NMP (*N*-Methyl pyrrolidone), and water. When DMF and DMSO were used as solvent, the yields fell markedly to 56% (DMSO) and 26% (DMF), respectively. NMP was another suitable solvent for the system, giving a good yield of 78% at 80 °C for 24 h (Table 1, entry 6). Meanwhile, almost no conversion was observed when water was used as solvent, which was probably due to its inefficiency in dissolving some of the starting materials (Table1, entry 8). In addition, attempts to reduce the quantities of copper(I) iodide and sodium ascorbate decreased the yield of 1,4-disubstituted 1,2,3-triazoles (Table1, entry 9), whereas adding more equivalents of copper(I) iodide and sodium ascorbate showed no further effects (Table 1, entry 10). On

the basis of these experiments, we concluded that the reaction proceeded most efficiently and was completed in 3 h when it was promoted by copper(I) iodide (0.2 equiv.) and sodium ascorbate (0.4 equiv.) in the presence of DBU (1 equiv.) by using HMPT as the solvent at 80 °C (Table 1, entry 4).

Having the optimized conditions in hand, we then examined the substrates scope of the one-pot synthesis of 1, 4-disubstituted 1,2,3-triazoles. The starting materials of *anti*-3-aryl-2,3-dibromopropanoic acids were easily prepared by bromination of the corresponding trans-unsaturated carboxylic acids.[9] Results summarized in Table 2 show that the method can be used for the synthesis of 1,4-disubstituted 1,2,3-triazoles carrying either electron-donating groups, such as methyl, ethyl, and methoxy (Table 2, entries 3–5), or electron-withdrawing groups, such as bromo, chloro, fluoro, and nitro on the aromatic ring of *anti*-3-aryl-2,3-dibromopropanoic acids (Table 2, entries 6–9). Meanwhile, this method proved to be applicable to substrate **1** bearing an *ortho*-formyl group, which gave the corresponding product **3b** at 53% yield. (Table 2, entry 2). Notably, the reaction of the pyridyl-substituted substrate **2** also proceeded smoothly, giving a moderate yield of 73%. (Table 2, entry 10).

The proposed mechanism for the reaction of *anti*-3-aryl-2,3-dibromopropanoic acids and nitrobenzaldehydes is shown in Scheme 2. Organic azide **4** and aryl alkyne **5** were supposed to be generated *in situ* and then combined into 1,2,3-triazoles **3** by

Cu(I)-catalyzed 1,3-dipolar cycloaddition. We conducted a control experiment with *anti*-3-aryl-2,3-bromopropanoic acid **2** under the optimized conditions and in the absence of sodium azide. The corresponding terminal alkyne **5** was obtained with a 94% yield. This result indicates that an alkyne was generated in the one-pot process probably by the debrominative decarboxylation of the *anti*-3-aryl-2,3-bromopropanoic acid **2** and subsequent elimination of hydrogen bromide in the presence of the base. Obviously, the organic azide **4** was obtained simultaneously from the S_NAr reaction of nitrobenzaldehydes **1** and sodium azide[10] (Scheme 2).

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 in DMSO-d_6 or $CDCl_3$ with TMS as the internal standard by using a Bruker AV400 spectrometer. Elemental analyses were performed using a Perkin-Elmer 2400 CHNS elemental analyzer. Mass spectra were obtained using a Finnigan MAT-95 mass spectrometer. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC on Huanghai GF 254 silica gel-coated plates. Column chromatography was carried out on 100-200 mesh silica gel at medium pressure. The *anti*-3-aryl-2,3-dibromopropanic acids **2** were synthesized according to literature procedures.[9]

General Procedure For The Synthesis Of 1,2,3-Triazoles (3a-J)

The solution of *o/p*-nitrobenzaldehyde (151 mg, 1 mmol), NaN_3 (130 mg, 2 mmol), *anti*-3-aryl-2,3-bromopropanoic acid (1mmol), CuI (38 mg, 0.2 mmol), DBU (152 mg, 1 mmol) and Na ascorbate (80 mg, 0.4 mmol) in HMPT (3 mL) was stirred in a round-bottom flask. The mixture was heated to the temperature indicated in Table 2 until the starting *o/p*-nitrobenzaldehyde was completely consumed (monitored by TLC). The reaction mixture was allowed to cool to r.t., and H_2O (15 mL) was added. The mixture was extracted with CH_2Cl_2 or $CHCl_3$ (3 × 20 mL). The combined organic layers were washed with sat. brine (3 × 30 mL), dried over $MgSO_4$, and the solvents removed under reduced pressure to provide the crude product, which was purified via flash chromatography (silica gel, particle size 100-200 mesh, n-hexane-CH_2Cl_2) or crystallized by EtOAc-EtOH.

Spectral Characterization Of 3i

Compound 4-(4-(4-nitrophenyl)-1H-1,2,3-triazol-1-yl)benzaldehyde (**3i**): Brown solid, mp: 270.2-270.9 °C. IR (KBr): 3142, 3105, 1697, 1601, 1509, 1400 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 10.11 (s, 1H), 9.74 (s, 1H), 8.40 (d, J = 7.5 Hz, 2H), 8.21 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 192.61, 147.53, 146.21, 140.72, 136.83, 136.45, 131.84, 126.74, 125.04, 122.51, 120.87. MS (ESI): m/z 295 $(M+H)^+$. Anal. Calcd. for $C_{15}H_{10}N_4O_3$: C, 61.22; H, 3.43; N, 19.04. Found: C, 61.18; H, 3.26; N, 19.15.

CONCLUSIONS

In conclusion, we developed a simple and efficient one-pot method for the preparation of 1,4-disubstituted 1,2,3-triazoles from *anti*-3-aryl-2,3-dibromopropanoic acids and nitrobenzaldehydes catalyzed by using copper(I) iodide in moderate to high yields. The process possesses considerable advantages in terms of its product diversity, mild reaction conditions, and the use of precursors instead of terminal alkynes and organic azides. Further studies on the application of the present methodology to the synthesis of biological active compounds are currently ongoing.

SUPPLEMENTARY MATERIAL

Full experimental detail, ^{1}H and ^{13}C NMR spectra for this article can be found via the "Supplementary Content" section of this article's webpage.

ACKNOWLEDGEMENT

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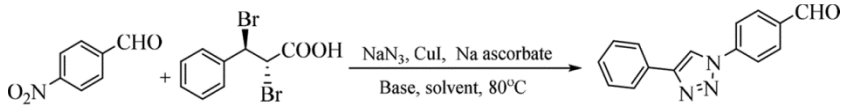
Table 1. Optimization of the synthesis of

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



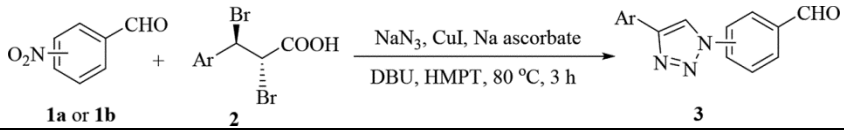
1a **2a** **3a**

Entry	CuI (equiv)	Sodium ascorbate (equiv)	Solvent	Base	Time (h)	Yield[b] of 3a (%)
1	0.2	0.4	HMPT	Ce_2CO_3	24	55
2	0.2	0.4	HMPT	K_2CO_3	24	34
3	0.2	0.4	HMPT	Et_3N	24	0
4	0.2	0.4	HMPT	DBU	3	88
5	0.2	0.4	DMSO	DBU	24	56
6	0.2	0.4	NMP	DBU	24	78
7	0.2	0.4	DMF	DBU	24	26
8	0.2	0.4	H_2O	DBU	24	0
9	0.1	0.2	HMPT	DBU	3	78
10	0.3	0.6	HMPT	DBU	3	86

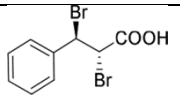
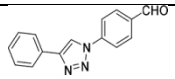
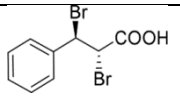
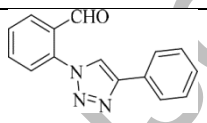
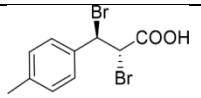
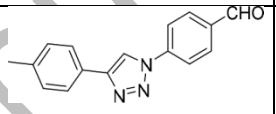
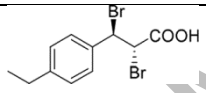
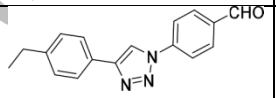
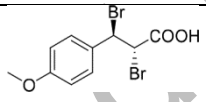
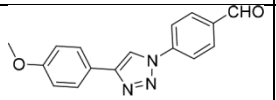
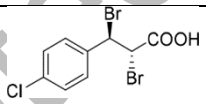
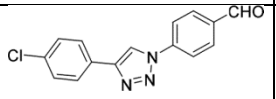
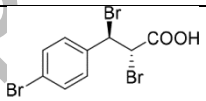
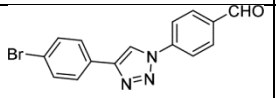
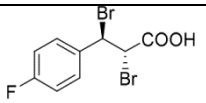
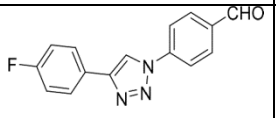
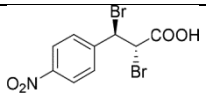
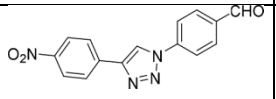
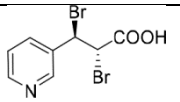
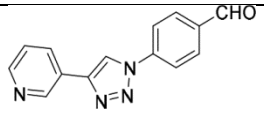
[a]Reaction conditions: Aldehyde **1a** (1 mmol), **2a** (1 mmol), NaN_3 (2 mmol), CuI (0.1~0.3 mmol), sodium ascorbate (0.2~0.6 mmol), and base (1 mmol) in solvent (3 mL);

[b]Isolated yields.

Table 2. Preparation of 1,4-disubstituted 1,2,3-triazoles containing formyl group (**3**)[a]



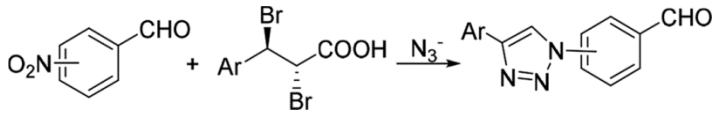
1a or **1b** **2** **3**

Entry	Aldehyde **1**	Alkynes **2**	Product **3**		Yield[b] of 3 (%)
1	**1a**		**3a**		88
2	**1b**		**3b**		53
3	**1a**		**3c**		81
4	**1a**		**3d**		85
5	**1a**		**3e**		87
6	**1a**		**3f**		80
7	**1a**		**3g**		84
8	**1a**		**3h**		77
9	**1a**		**3i**		68
10	**1a**		**3j**		73

[a]Reaction conditions: Aldehyde **1** (1 mmol), NaN_3 (2 mmol), Substrate **2** (1 mmol), CuI (0.2 mmol), sodium ascorbate (0.4 mmol), and DBU (1 mmol) in HMPT (3 mL);

[b]Isolated yields.

Scheme 1. One-pot synthesis of 1,2,3-triazoles from *anti*-3-aryl-2,3-dibromopropanoic acids and nitrobenzaldehydes.



Scheme 2. The proposed mechanism for the reaction of *anti*-3-aryl-2,3-dibromopropanoic acids and nitrobenzaldehydes.