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PII: S0040-4039(18)31031-1
DOI: https://doi.org/10.1016/j.tetlet.2018.08.039
Reference: TETL 50214

To appear in: *Tetrahedron Letters*

Received Date: 20 June 2018
Revised Date: 13 August 2018
Accepted Date: 20 August 2018

Please cite this article as: Li, L., Xing, X., Zhang, C., Zhu, A., Fan, X., Chen, C., Zhang, G., Novel synthesis of 5-iodo-1,2,3-triazoles using an aqueous iodination system under air, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.08.039

Graphical Abstract

Novel synthesis of 5-iodo-1,2,3-triazoles using an aqueous iodination system under air

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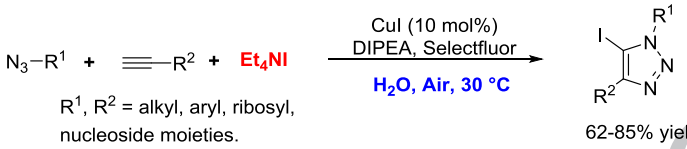

- *Inexpensive and simple iodine reagent*
- *High functional group tolerance*
- *Water solvent and open air*
- *Broad substrate scope*

Tetrahedron Letters
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Novel synthesis of 5-iodo-1,2,3-triazoles using an aqueous iodination system under air

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Iodination in water
5-iodo-1,2,3-triazoles
Nucleosides

ABSTRACT

A novel aqueous iodination system was developed for the synthesis of 5-iodo-1,2,3-triazoles under air. This reaction system has high efficiency and excellent chemo-selectivity with wide functional group tolerance. In addition, this method can be utilized for the modification of biomolecules such as riboses and nucleosides, and for the double labeling of biomolecules when coupled with other reaction types such as the Sonogashira reaction. 2009 Elsevier Ltd. All rights reserved.

1,2,3-Triazoles are important pharmacophores which have been widely used in medicinal chemistry.[1,2] Among them, 5-functionalized 1,2,3-triazoles show many privileged properties and have been utilized as high-affinity Hsp90 inhibitors,[3] potent antileukemic lead compounds,[4] and chiral ligands.[5] 5-Iodo-1,2,3-triazoles also display biological activities (Fig. 1A),[6] and have also been used as platform molecules for further functionalization.[7,8] Numerous efforts have been made for the synthesis of various functionalised 5-iodo-1,2,3-triazoles.[9-11] Multicomponent syntheses involving copper-catalyzed alkyne/azide cycloaddition (CuAAC) have shown high regiospecificity at the 5-position of the 1,2,3-triazole, as well as high atom- and step-economy, but the key intermediate copper triazolides are easily attacked by water or oxidized by oxygen (Fig. 1B).[12-14] Therefore, these reactions are typically conducted under an inert atmosphere with anhydrous reaction conditions,[15-17] and in some cases utilise expensive ligands for the control of reaction selectivity.[18,19]

In the past few years, researchers have investigated the multicomponent syntheses of 5-iodo-1,2,3-triazoles in water.[20, 21] These methods have advantages such as readily accessible starting materials and clean reaction media, but they still suffer from narrow substrate scope, high reaction temperatures, use of additive agents, and limited iodine

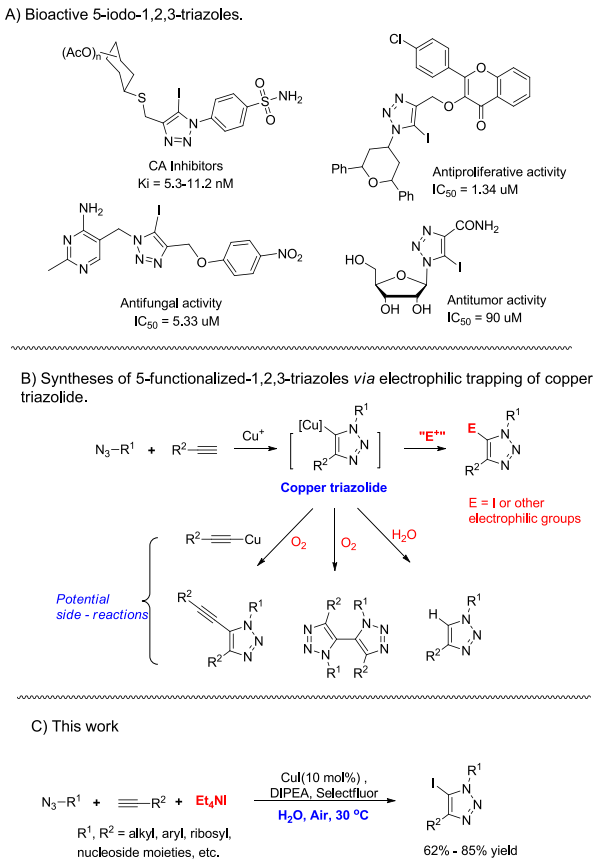

Figure 1. 5-iodo-1,2,3-triazoles and their synthesis.

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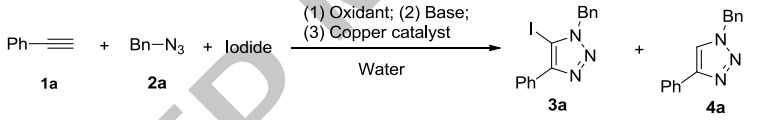
sources. Herein, we report that the iodine source has a significant influence on the chemoselectivity for the synthesis of 5-iodo-1,2,3-triazoles. When Et_4NI was used as the iodine source, the target 5-iodo-1,2,3-triazoles were obtained in good to high isolated yields in aqueous solutions under air, and potential side-reactions, including the protonation and oxidation of copper triazolides, are effectively inhibited (Fig. 1C).

The model reaction between benzyl azide **1a** and phenylacetylene **2a** was selected to study the influence of the iodine source (Table 1). When sodium iodide was used the protonation product of copper triazolides, 5-*H*-1,2,3-triazole **4a**, was the main product (60%) and the target compound 5-iodo-1,2,3-triazole **3a** was only obtained in 32% yield (Table 1, entry 1).[20] When quaternary ammonium iodides were utilized the yields of **3a** was significantly increased (Table 1, entries 2-6). Specifically, with Et_4NI the target compound **3a** was obtained in 82% yield. However, quaternary ammonium iodides bearing propyl and butyl groups showed a slight decrease in the yield of **3a.** The influence of bases (Table 1, entries 7, 8), oxidants (Table 1, entries 9-19) and catalysts (Table 1, entries 20, 21) were also studied. The influence of the temperature was also investigated (Table 1, entries 1, 22, 23) and 30 ^{o}C was found to be optimal. The results in Table 1 also indicated that the replacement of water with methanol as the solvent completely inhibited the formation of triazole **3a** (Table 1, entry 24).

The optimized reaction conditions were then utilized for the synthesis of various 5-iodo-1,2,3-triazoles (Table 2). Aryl alkynes bearing either electron-donating groups or electron-withdrawing groups reacted with azide **2a** to afford the corresponding products in good to high yields (Table 2, entries 1-4). Aliphatic alkyne **1e** also gave the target 5-iodo-1,2,3-triazole **3e** in satisfactory yield (Table 2, entry 5). The substrate tolerance with respect to the azide (Table 2, entries 6-11), showed that alkyl azides, phenyl azides and benzyl azides were all suitable substrates, and that the substituent on the benzyl ring had no significant influence on their reactivity.

Nucleosides bearing 1,2,3-triazole motifs are widely used in medicinal chemistry.[6,22] Therefore, our aqueous reaction system was expanded to the modification of riboses and nucleosides with the iodo-1,2,3-triazole motif (Table 2). Azide substituted uridines and riboses with different protecting groups reacted with phenylacetylene **1a** to give the corresponding 5-iodo-1,2,3-triazole nucleosides, with the ribose ring and the protecting groups remaining intact. Alkyne substituted uridines, with or without protecting groups, also reacted effectively with benzyl azide **2a** (Table 2, entries 15 and 16). These results demonstrated that nucleosides bearing either azide or alkyne groups could be converted to the corresponding 5-iodo-1,2,3-triazole derivatives, implying that this method could provide broad classes of nucleoside derivatives as candidate compounds for drug discovery.

Table 1. Optimization of the reaction conditions for the synthesis of 5-iodo-1,2,3-triazoles in an aqueous solvent.[a]

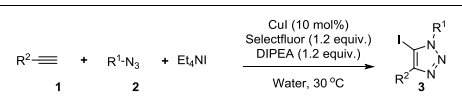


1a 2a 3a 4a

Entry	Iodide source	Base	Oxidant	Catalyst	Temp (°C)	Time (h)	Yield[b]	
							3a (%)	**4a (%)**
1	NaI	DIPEA	Selectfluor	CuI	30	3	32	60
2	NH_4I	DIPEA	Selectfluor	CuI	30	3	65	31
3	Me_4NI	DIPEA	Selectfluor	CuI	30	3	70	25
4	**Et_4NI**	**DIPEA**	**Selectfluor**	**CuI**	**30**	**3**	**82**	**14**
5	Pr_4NI	DIPEA	Selectfluor	CuI	30	3	60	32
6	Bu_4NI	DIPEA	Selectfluor	CuI	30	3	58	37
7	Et_4NI	Cs_2CO_3	Selectfluor	CuI	30	3	22	33
8	Et_4NI	K_2CO_3	Selectfluor	CuI	30	3	52	31
9	Et_4NI	DIPEA	ChloramineT	CuI	30	3	68	25
10	Et_4NI	DIPEA	NIS	CuI	30	3	36	51
11	Et_4NI	DIPEA	NBS	CuI	30	3	45	36
12	Et_4NI	DIPEA	DDQ	CuI	30	3	18	76
13	Et_4NI	DIPEA	*m*-CPBA	CuI	30	3	29	54
14	Et_4NI	DIPEA	TBHP	CuI	30	3	48	36
15	Et_4NI	DIPEA	DTBP	CuI	30	3	5	69
16	Et_4NI	DIPEA	DCP	CuI	30	3	3	68
17	Et_4NI	DIPEA	BPO	CuI	30	3	5	72
18	Et_4NI	DIPEA	$CuCl_2$	CuI	30	3	10	79
19	Et_4NI	DIPEA	NaClO	CuI	30	3	25	62
20	Et_4NI	DIPEA	Selectfluor	CuBr	30	3	31	35
21	Et_4NI	DIPEA	Selectfluor	CuCl	30	3	20	26
22	Et_4NI	DIPEA	Selectfluor	CuI	10	24	60	31
23	Et_4NI	DIPEA	Selectfluor	CuI	50	3	54	33
24	Et_4NI	DIPEA	Selectfluor	CuI	30	3	-	-[c]

[a] Reagents and conditions: alkyne **1a** (0.1 mmol), azide **2a** (0.11 mmol), iodide source (0.11 mmol), oxidant (0.12 mmol), copper catalyst (0.01 mmol), H_2O (0.5 mL).[b] Isolated yield. [c] Methanol was used as the solvent under air.

Table 2. Multi-component synthesis of 5-iodo-1,2,3-triazoles.

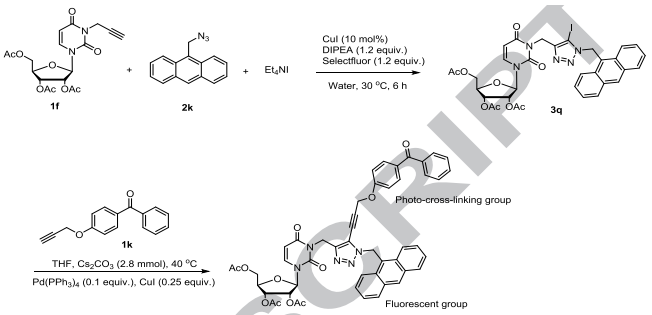


Entry[a]	Alkynes	Azides	Product	Time (h)	Yield **3** (%)
1	**1a**	**2a**	**3a**	3	82
2	**1b**	**2a**	**3b**	3	85
3	**1c**	**2a**	**3c**	3	86
4	**1d**	**2a**	**3d**	4	71
5	**1e**	**2a**	**3e**	4	73
6	**1a**	**2b**	**3f**	4	77
7	**1a**	**2c**	**3g**	3	83
8	**1a**	**2d**	**3h**	3	85
9	**1a**	**2e**	**3i**	3	81
10	**1a**	**2f**	**3j**	3	82
11	**1a**	**2g**	**3k**	5	76
12	**1a**	**2h**[c]	**3l**[c]	5	69
13	**1a**	**2i**[c]	**3m**[c]	5	62
14	**1a**	**2j**	**3n**	5	71
15	**1f**	**2a**	**3o**	5	65
16	**1g**	**2a**	**3p**	5	63

[a] Reagents and conditions: alkyne (0.1 mmol), azide (0.11 mmol), Et_4NI (0.11 mmol), Selectfluor (0.12 mmol), DIPEA (0.12 mmol), CuI (0.01 mmol), H_2O (0.5 mL), 3-5 h , 30 °C. [b] Isolated yield. [c] β-isomer.

The successful utilization of our reaction system in riboses and nucleosides promoted us to investigate its use in the double labelling of a representative nucleoside. Propargyl uridine **1f** was first reacted with fluorescent 9-(azidomethyl)anthracene **2k** to give the fluorescent compound **3q**. Next, an alkyne with a photo-cross-linking group **5a** was reacted with **3q** *via* the Sonagashira reaction, giving the double labelled nucleoside **5a** in 78% overall yield (Scheme 1). This application indicated our method is potentially appropriate for the modification of structurally complicated biomolecules with multi-functionalised groups.

Scheme 1. Fluorescent and photo-cross-linking dual labelling of a nucleoside based on 5-iodo-1,2,3-triazoles.

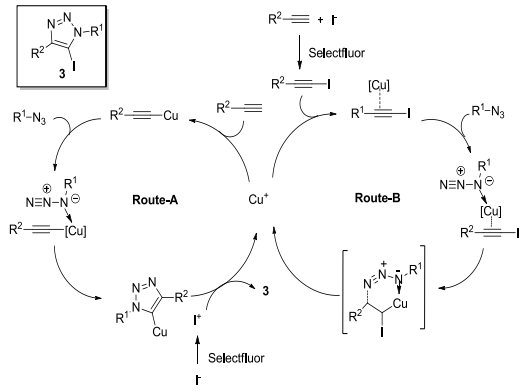


A series of control experiments were then conducted to investigate the plausible mechanism. Two separate mechanistic pathways proceeding *via* the 1-iodoalkyne or the triazolide copper species were suggested (Route A and B, Scheme 2).[23] We first investigated whether the triazolide copper species existed in the current reaction system. After the addition of allyl bromide (4.0 equiv.), 5-allyl-1,2,3-triazole was obtained in 25% yield (Eq 1, Scheme 2), suggesting the existence of an intermediate triazolide copper species.[23a] Next, we studied the possibility of 1-iodoalkyne as a reaction intermediate. When the azide component was omitted from the optimized reaction conditions, 1-iodoalkyne was obtained in 88% yield (Eq 2, Scheme 2). After benzyl azide was added again, the formed 1-iodoalkyne reacted to give 5-iodo-1,2,3-triazole in 86% yield (Eq 3, Scheme 2). Based on the results of Eq 2 and Eq 3, Route B represents the most reasonable pathway.

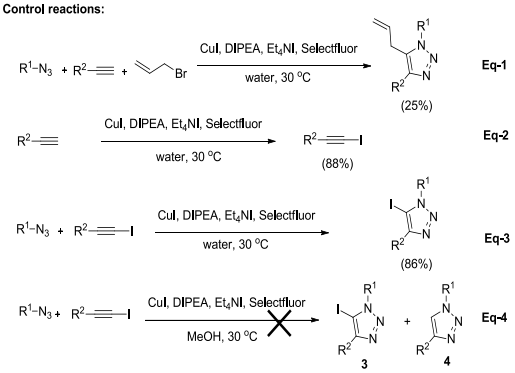
In addition, we investigated the roles of water and the quaternary ammonium iodide. When Et_4NI added to a mixture of the alkyne, azide and catalyst in an aqueous solvent, a suspension was formed from the formerly biphasic mixture (Image A and B, Scheme 2). After reaction completion, the mixture again turned bi-phasic (Image C, Scheme 2). This suggested that a micro-hydrophobic core might be formed around the catalytic Cu(I) species in the suspension, which could increase its stability and promote the cycloaddition reaction between the alkyne or 1-iodoalkyne and the azide in water. When methanol was added to the aqueous reaction to break-up the formed suspension, no 5-*H*-1,2,3-triazole or 5-iodo-1,2,3-triazole was detected (Eq 4, Scheme 2), The UV spectrum of the methanol-water reaction mixture further showed an absorption at 700 nm, indicating that Cu(I) had been oxidised into Cu(II).[23a]

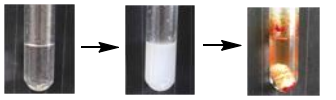
In summary, an efficient oxidative iodination system was developed for the synthesis of 5-iodo-1,2,3-triazoles in water. This method showed excellent functional group tolerance and could be utilized for the modification of biomolecules such as nucleosides and riboses. Further utilization in the double labeling of biomolecules suggested that this method can also be coupled with other type of reactions such as the Sonagashira reaction to allow multi-functional modifications.

Scheme 2. Possible reaction mechanism.



Control reactions:





(A) Before addition of the iodine source
(B) After addition of the iodine source and oxidant
(C) Reaction completion

Acknowledgments

This work was supported by the National Natural Science Foundation of China (21472036), Excellent Youth Foundation of Henan Scientific Committee (164100510020)

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Supplementary Materia

Supplementary data associated with this article can be found, in the online version at Supporting Information (ESI).

Highlights

Multi-component iodination reaction in water under open air.

Syntheses of 5-iodo-1,2,3-triazoles from inexpensive and simple starting materials.

Quaternary ammonium iodide (QAI) regulates chemoselectivity.

Modification and labeling of biomolecules.