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Dong Wang, Si Chen, Baohua Chen

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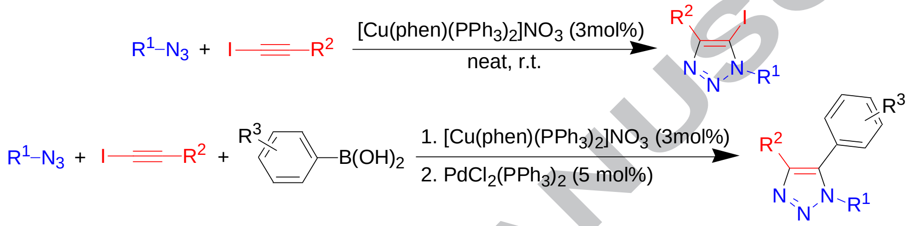

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“Green” synthesis of 1,4-disubstituted 5-iodo-1,2,3-triazoles under neat conditions, and an efficient approach of construction of 1,4,5-trisubstituted 1,2,3-triazoles in one pot

Dong Wang,§ Si Chen,§ and Baohua Chen∗

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, 730000, P. R. China; Key Laboratory of Nonferrous Metal Chemistry and Resources Utilization of Gansu Province, Lanzhou, 730000, P. R. China

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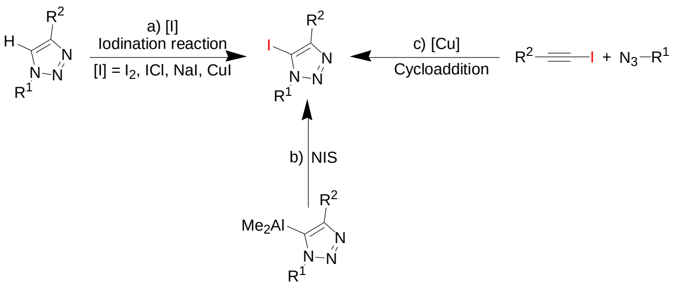
ABSTRACT

An environmentally friendly and efficient method for synthesis of 1,4-disubstituted 5-iodo-1,2,3-triazoles through [Cu(phen)$(PPh_3)_2$]NO_3-catalyzed cycloaddition of organic azides and iodoalkynes under solvent-free conditions was developed. Based on this, a one-pot method for the synthesis of fully substituted 1,2,3-triazoles via cycloaddition/Suzuki reactions was also demonstrated in this report.

The copper-catalyzed alkyne-azide cycloaddition reaction (CuAAC)[1, 2] yielding 1,2,3-triazoles under mild conditions with high efficiency is undoubtedly the premier example of a “click chemistry” to date,[3] it has been widely applied in various fields including chemical synthesis, biology, medical science and material science.[4] However, CuAAC is limited to terminal alkynes with the production of 1,4-disubstituted triazoles. Until now only a few methods,[5] for example, ruthenium-catalyzed cycloaddition of internal alkynes with organic aizdes,[5a] were developed for the synthesis of fully substituted (trisubstituted) 1,2,3-triazoles, which possess various promising applications as multifunctional bioactive molecules, and in material science. These reported methods are not really modeled reactions, only partially address deficiency of CuAAC. Therefore, a general method for synthesis of fully substituted 1,2,3-triazoles would be a valuable addition to existing strategies.

Due to the existence of highly reactive 5-iodo fragment, 5-iodo-triazoles are versatile synthetic intermediates that provide the possibility of straightforward introduction of another functionalized fragment into 1,2,3-triazoles unit.[6] Several known methods for the synthesis of 5-iodo-triazoles can be classified into three types (Scheme 1): a) iodination of 1,4-disubstituted 1,2,3-triazoles;[7] b) iodination of 1,4-disubstituted 5-alumino-1,2,3-triazoles;[8] c) copper-catalyzed cycloaddition of 1-iodoalkynes with organic azides.[9] The latter is the most efficient, economical, easy-to-operate, highly selective synthetic strategy comparing with the former two. It should be pointed out that the reported methods of copper-catalyzed cycloaddition of 1-iodoalkynes with organic azides generally involve organic solvents such as DMSO, THF and CH_3CN. Owing to the environmental harmfulness of organic solvents, it is highly desirable to develop more environmentally friendly and economic methodologies for synthesizing 5-iodo-triazoles.



Scheme 1. General strategy for the synthesis of 1,4-disunstituted 5-iodo-1,2,3-triazoles.

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§ Both authors contributed equally to this work.

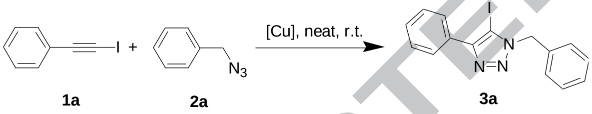
∗ Corresponding author. Tel.: +86-139-198-15840; fax: +86-931-891-2582; e-mail: chbh@lzu.edu.cn

We recently demonstrated the remarkable activity of $[Cu(phen)(PPh_3)_2]NO_3$ complex (phen=1,10-phenanthroline) in the Huisgen cycloaddition of terminal alkynes with organic azides.[10] Herein, we report that 1-iodoalkynes are also suitable cycloaddition partners taking the place of terminal alkynes in the presence of $[Cu(phen)(PPh_3)_2]NO_3$ complexes under “green” solvent-free conditions, offering 5-iodo-1,2,3-triazoles. In addition, fully substituted 1,2,3-triazoles can be successfully synthesized through cycloaddition/Suzuki reactions of organic azides and iodoalkynes, and borophenylic acid in one pot.

In the initial survey of experimental conditions, iodoethynyl-benzene **1a** and benzyl azide **2a** were chosen as the model substrates, and the cycloaddition was conducted at room temperature in air under solvent-free conditions for 24 h in the presence of several Cu(I) salts and complexes with 1mol% of catalytic amount. It was observed that Cu(I) salts CuBr and CuI were not effective for this transformation, the desired product **3a** was obtained in nearly 0 and 7% yields, respectively (Table 1, entries 5 and 6). The uses of Cu(I) complexes including $Cu(PPh_3)_3Br$, $Cu(PPh_3)_3Cl$, $Cu(PPh_3)_2NO_3$, $[Cu(phen)(PPh_3)_2]NO_3$ provided 29-54% yields, and among of them, $[Cu(phen)(PPh_3)_2]NO_3$ showed superior catalytic activity (entries 1-4). The yields increased gradually with raising the catalyst loadings or reaction time (entries 7-9). When the reaction was carried out in the presence of 3 mol% $[Cu(phen)(PPh_3)_2]NO_3$ within 36 hours, the corresponding 5-iodo-1,2,3-triazole **3a** was isolated with 86% yield and 100% selectivity (entry 9). In addition, we found that the catalytic system was successfully and reproducibly applied up to 10 mmol-scale synthesis, allowing the isolation of 2.63 g (73% yield) of **3a** (entry 10).

Table 1

Screening of catalysts for cycloaddition reaction between iodoethynyl-benzene and benzyl azide.[a]



Entry	Catalyst (mol%)	Time (h)	Yield (%)[b]
1	$Cu(PPh_3)_3Br$ (1)	24	29
2	$Cu(PPh_3)_3Cl$ (1)	24	31
3	$Cu(PPh_3)_2NO_3$ (1)	24	37
4	$[Cu(phen)(PPh_3)_2]NO_3$ (1)	24	54
5	CuBr (1)	24	Trace
6	CuI (1)	24	7
7	$[Cu(phen)(PPh_3)_2]NO_3$ (2)	24	65
8	$[Cu(phen)(PPh_3)_2]NO_3$ (3)	24	75
9	$[Cu(phen)(PPh_3)_2]NO_3$ (3)	36	86
10	$[Cu(phen)(PPh_3)_2]NO_3$ (3)	36	73[c]

[a] The reaction was carried out using **1a** (0.5 mmol) and **2a** (0.5 mmol) in the presence of a catalyst at room temperature in air.

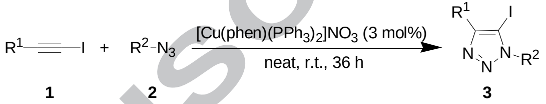
[b] Isolated yields after column chromatography.

[c] The reaction is carried out in 10 mmol of scale.

Encouraged by the efficiency of the reaction protocol described above, we investigated the substrate scope. A series of terminal alkynes were investigated to be reacted with benzyl azide under the optimized conditions. As shown in Table 2, both aromatic and aliphatic alkynes were suitable cycloaddition partners, the corresponding 1,4-disubstituted 5-iodo-1,2,3-triazoles were synthesized with the yields in the range of 69-91%, and the reactivity of aliphatic alkyne (Table 2, entry 9) was somewhat lower than aromatic ones (entries 1, 4, 5, 7). The reaction of the heteroatomcontaining alkynes 3-ethylthiopheen with benzyl azide proceeded efficiently, the corresponding 1,4-disubstituted-5-iodo-1,2,3-triazoles **3g** was isolated in 91% yield (entry 7). The substrate scope of organic azides was also examined. The results indicated that aliphatic azides including benzyl, *n*-octyl, *n*-dodecyl, and 4-nitrobenzyl groups were successfully employed, and the reactivities of both *n*-octyl and *n*-dodecyl azides were lower than the azides containing benzyl group. In addition, the longer chain of aliphatic azide can slow down the process (entries 2 and 3). Unfortunately, only trace product was obtained when the phenyl azide was employed (entry 10).

Table 2

Screening of catalysts for cycloaddition reaction between 1-iodoalkynes and organic azides.[a]

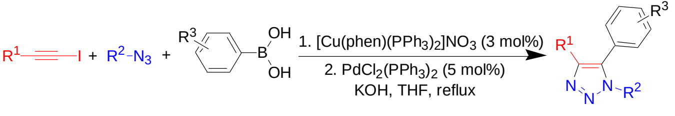


Entry	R^1	R^2	Product	Yield (%)[b]
1	Ph	$PhCH_2$	**3a**	86
2	Ph	C_8H_{17}	**3b**	57
3	Ph	$C_{12}H_{25}$	**3c**	32
4	4-CH_3Ph	$PhCH_2$	**3d**	76
5	4-CH_3OPh	$PhCH_2$	**3e**	77
6	4-CH_3OPh	4-NO_2PhCH_2	**3f**	88
7	Thiophen-3-yl	$PhCH_2$	**3g**	91
8	Thiophen-3-yl	C_8H_{17}	**3h**	87
9	C_4H_9	$PhCH_2$	**3i**	69
10	Ph	Ph	**3j**	Trace

[a] The reaction was carried out using **1** (0.5 mmol) and **2** (0.5 mmol) in the presence of $[Cu(phen)(PPh_3)_2]NO_3$at room temperature within 36 h in air.

[b] Isolated yields after column chromatography.

The cascade reaction strategy offers significant advantages over classical stepwise methods and has widely been used as a powerful protocol in organic synthesis, because it offers rapid and convergent construction of molecules without the need of isolation and purifications of any intermediates.[11] Suzuki-Miyaura cross-coupling reaction has proven to be a powerful tool for assembling two fragments into one molecular through the formation of carbon-carbon bonds under milder conditions. In this context, a three-component one-pot process was explored through cycloaddition/Suzuki-Miyaura reactions of organic azides, iodoalkynes, and borophenylic acid (Scheme 2). This sequential process was conducted nicely in the presence of 3 mol% of $[Cu(phen)(PPh_3)_2]NO_3$ and 5 mol% of $PdCl_2(PPh_3)_2$ using KOH as base in refluxing THF. The desired 1,4,5-trisubstituted 1,2,3-triazoles **4a-4d** bearing various groups were obtained in 74-83% yields.



4a: R^1 = Ph, R^2 = $PhCH_2$, R^3 = H; yield = 78%
4b: R^1 = Ph, R^2 = $PhCH_2$, R^3 = 4-CH_3; yield = 74%
4c: R^1 = Ph, R^2 = C_6H_7, R^3 = H; yield = 80%
4d: R^1 = C_4H_9, R^2 = $PhCH_2$, R^3 = H; yield = 83%

Scheme 2. Synthesis of 1,4,5-trisubstituted-1,2,3-triazoles in “one-pot”.

In summary, an environmentally friendly method for synthesis of 1,4-disubstituted 5-iodo-1,2,3-triazoles through [Cu(phen)(PPh$_3$)$_2$]NO$_3$-catalyzed cycloaddition of organic azides and iodoalkynes under solvent-free conditions were developed. Nine 1,4-disubstituted 5-iodo-1,2,3-triazoles were produced in up to 91% yields. On the basis of this neat synthesis, a series of fully substituted 1,2,3-triazoles were readily obtained through a sequential process involving cycloaddition and Suzuki reaction. The procedures reported in this work are economical and performed easily, making them possibly acceptable for industrial-scale production. The presented method will be perhaps applied in the syntheses of modified 1,2,3-triazolyl bioactive molecules, 1,2,3-triazolyl multi-functional materials, and multi-dentate organic ligands containing 1,2,3-triazole.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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