



A mild copper-mediated Glaser-type coupling reaction under the novel CuI/NBS/DIPEA promoting system

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ARTICLE INFO

Article history:

Received 24 February 2009

Revised 9 April 2009

Accepted 17 April 2009

Available online 22 April 2009

ABSTRACT

A simple copper promoting system CuI/NBS/DIPEA was first found to efficiently promote Glaser coupling reaction under ambient temperature. The alkynes with sensitive groups such as acetal and ketal, TBDMS, ester and amide could react smoothly to afford the functionalized 1,3-diynes under the CuI/NBS/DIPEA promoting system in good yields. And the successful application of the CuI/NBS/DIPEA promoting system in sugar and amino acid-building blocks indicated the potential of this method in the construction of designed sugar and peptide biomolecules.

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1. Introduction

Recently, copper-mediated coupling reactions have raised great attention in natural products and designed biomolecules synthesis.^{1,2} One of the reasons is the key discovery that some organic derivatives can speed up the traditional copper-mediated coupling reaction and make these coupling reactions under mild conditions, which allow the copper-mediated coupling reaction to be used well in end game strategies on complex substrate.¹ The Glaser-type coupling is a classic reaction to prepare 1,3-diynes through homocoupling reaction from terminal alkynes. Glaser-type coupling reactions have been applied in numerous research fields from total synthesis of polyynes natural products to the straightforward elaboration of highly conjugated new materials.^{3–16} The current methods for the Glaser-type coupling mainly include traditional copper-mediated Glaser-type coupling reactions,^{5–10} and Palladium-assisted Glaser-type coupling reactions.^{11–16} The traditional copper-mediated Glaser-type coupling reactions usually involved excessive oxidants,^{6,7} rigid inorganic base and high temperature,⁹ or expensive ionic liquid and supercritical CO₂.^{10a,b} Palladium-assisted Glaser-type coupling reactions mediated by Pd (0) or Pd (II), are arguably the most mild, efficient, and selective methods for the synthesis of 1,3-diynes.^{11,12,15} However palladium reagents are expensive, and often required air-sensitive and poisonous ligands. It is still a challenge to find new copper-mediated promoting systems for the mild Glaser-type coupling reaction with diverse structures.

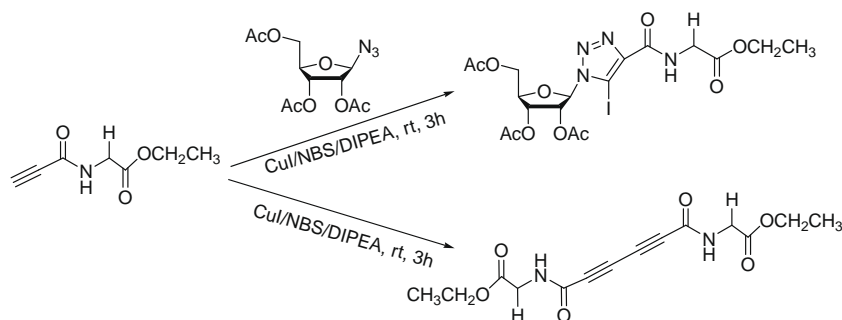
Recently, we found that CuI/NBS/DIPEA could promote terminal alkynes and azides to produce 5-I-1,4-substituted-1,2,3-triazoles with good chemoselectivity under mild conditions.¹⁷ On the fur-

ther investigation on this reaction procedure, we found that a new compound was produced in the absence of azide under the CuI/NBS/DIPEA promoting system (Scheme 1). This compound was firstly considered as the halo alkyne from the reaction of halo cation and alkyne copper in the reaction mixture, but ¹H NMR and MS showed that the new compound was the product of homocoupling reaction of terminal alkynes. In view of the good chemoselectivity of the CuI/NBS/DIPEA promoting system shown in the preparation of 5-I-1,4-substituted-1,2,3-triazoles, and the mild reaction conditions of this reaction, we tried to explore the potential of CuI/NBS/DIPEA promoting system as a novel palladium-free approach for Glaser-type coupling reaction of terminal alkynes. Here, we report that CuI/NBS/DIPEA as a simple copper promoting system is found to efficiently promote Glaser-type coupling reaction under very mild conditions, and this promoting system can be applied well in alkynes with sensitive functional groups and in sugar and amino acid-building blocks.

2. Results and discussion

The homocoupling reaction of 1-ethynylcyclohexanol was taken as an example for the optimization of the reaction conditions (as shown in Table 1). Firstly, the amount of CuI, NBS, and DIPEA was investigated and the best ratio of the substrates, CuI, NBS, and DIPEA was 1:0.5:0.5:1 (Table 1, entries 1–8). Different solvents were then investigated for this reaction, and acetonitrile was the best one with the highest yield in 4 h under ambient temperature, compared with acetone, THF, and ethanol (Table 1, entries 11–13). Finally, the reaction temperature was investigated. The ambient temperature (25 °C) was the best choice for this promoting homocoupling reaction, as the lower temperature made the reaction slow (Table 1, entry 14), and the high temperature reduced the

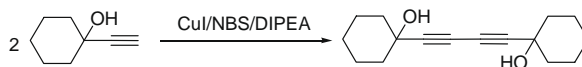
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Scheme 1. The reactions of alkyne with and without azide mediated by CuI/NBS/DIPEA.

Table 1

Screening reaction parameters for Glaser-type coupling reaction under CuI/NBS/DIPEA promoting system



Entry ^a	CuI (equiv)	NBS (equiv)	Base (equiv)	Solvent ^b	Temp (°C)	Time (h)	Yield (%) ^c
1	0.1	0.5	1	CH ₃ CN	rt	4	21
2	0.3	0.5	1	CH ₃ CN	rt	4	69
3	0.5	0.5	1	CH ₃ CN	rt	4	90
4	0.5	0.1	1	CH ₃ CN	rt	4	21
5	0.5	0.3	1	CH ₃ CN	rt	4	61
6	0.5	0.5	0.5	CH ₃ CN	rt	4	58
7	0.5	0.5	0.3	CH ₃ CN	rt	4	25
8	0.5	0.5	0.1	CH ₃ CN	rt	4	N.R. ^d
9	0.5	0.5	1	CH ₃ CN	rt	2	65
10	0.5	0.5	1	CH ₃ CN	rt	10	89
11	0.5	0.5	1	THF	rt	4	13
12	0.5	0.5	1	CH ₃ CH ₂ OH	rt	4	54
13	0.5	0.5	1	CH ₃ COCH ₃	rt	4	57
14	0.5	0.5	1	CH ₃ CN	0	4	78
15	0.5	0.5	1	CH ₃ CN	50	4	80

^a The Glaser-type coupling reaction of 1-ethynylcyclohexanol (1 mmol) was taken as the example for screening reaction parameters.

^b 3 mL Solvent was used for 1 mmol 1-ethynylcyclohexanol.

^c Isolated yield.

^d Alkyne was recovered.

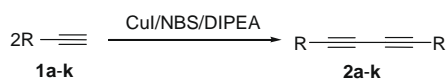
reaction yield. (Table 1, entry 15). After the above-mentioned optimization, the best result for homocoupling of 1-ethynylcyclohexanol with 90% isolated yield was afforded when the ratio of the substrates, CuI, NBS, and DIPEA was 1:0.5:0.5:1 at ambient temperature in CH₃CN for 4 h (Table 1, entry 3).

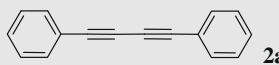
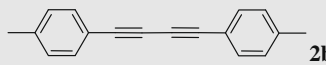
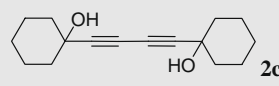
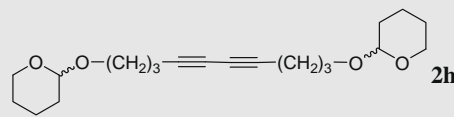
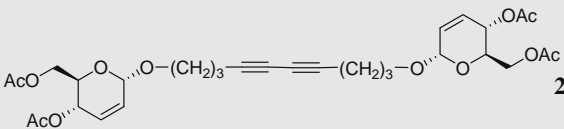
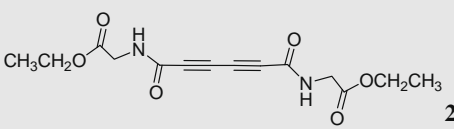
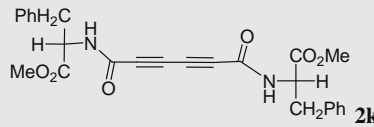
Under the optimized condition, the application of this new synthetic protocol was explored by using various alkynes as building blocks to construct 1,3-diynes derivatives (Table 2). Both aliphatic and aromatic terminal alkynes successfully underwent the homocoupling to produce the corresponding 1,3-diynes in good to excellent yields. Different types of protective groups, such as acid-sensitive groups (THP, glycosyl bond), alkali-sensitive acetyl, and TMDMS group could tolerate the reaction conditions. Some widely used functional groups such as ester, ether, amide, and hydroxyl were also found intact under the CuI/NBS/DIPEA promoting system. Furthermore, the alkynes in the sugar and amino acid-building blocks were tried under the CuI/NBS/DIPEA promoting systems, and the corresponding 1,3-diynes were successfully obtained in good yields with intact sugar and amino moieties, which illustrated the potential of this method in the construction of designed sugar and peptide biomolecules (Table 2, 2i–k).

As a novel copper promoting system, the two plausible mechanisms for the CuI/NBS/DIPEA-mediated Glaser coupling reaction

were proposed based on the reported mechanism for homocoupling reaction of terminal alkynes,¹⁹ and on our previous work.¹⁷ In the plausible route I (Scheme 2), Cu⁺-acetylide complex 4 could be produced from the Cu⁺-acetylide 3. Then an oxidative coupling reaction might take place to give coupling product 2 with NBS as the oxidant. Based on the plausible route I, several oxidants such as oxygen,^{6,7} DDQ²⁰, and iodine¹⁶ were chosen for the homocoupling reaction under ambient temperature instead of NBS, but no desirable product was obtained and the alkynes could be recovered completely. The nitrogen atmosphere was also used for this CuI/NBS/DIPEA promoting system and the desired 1,3-diynes were obtained, which excluded the possibility of the oxygen in air as the oxidant for this homocoupling reaction procedure. Thus the present CuI/NBS/DIPEA-mediated Glaser coupling reaction might have a reaction mechanism different from the reported oxidative homocoupling reaction of terminal alkynes. For the other plausible route II (Scheme 2), a mechanism through 1-halo alkyne intermediate 5 could be proposed. The Cu⁺-acetylide 3 could trap X⁺ from reaction mixture to give 1-halo alkynes 5. Once the intermediate 5 was produced, it could react immediately with Cu⁺-acetylide complex 3 from the reaction mixture, halo anion left, and then the coupling product 2 could be obtained.²¹

Table 2
CuI/NBS/DIPEA-mediated Glaser-type coupling reaction^a



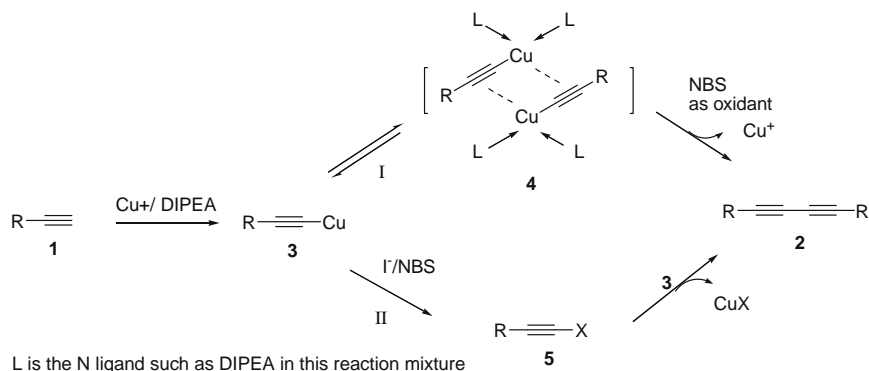
Reactants	Products ¹⁸	Time (h)	Isolated yield (%)
1a	 2a	2	93
1b	 2b	3	90
1c	 2c	4	90
1d	$\text{H}_3\text{C}-(\text{CH}_2)_5 \text{---} \equiv \equiv \text{---} (\text{CH}_2)_5-\text{CH}_3$ 2d	2	95 ^b
1e	$\text{HO}-(\text{CH}_2)_3 \text{---} \equiv \equiv \text{---} (\text{CH}_2)_3-\text{OH}$ 2e	3	94
1f	$\text{AcO}-(\text{CH}_2)_3 \text{---} \equiv \equiv \text{---} (\text{CH}_2)_3-\text{OAc}$ 2f	4	89
1g	$\text{TBDMSO}-(\text{CH}_2)_3 \text{---} \equiv \equiv \text{---} (\text{CH}_2)_3-\text{OTBDMS}$ 2g	4	89
1h	 2h	4	85
1i	 2i	4	78
1j	 2j	2	84
1k	 2k	2	83

^a All the reaction proceeded in CH_3CN under ambient temperature, and the ratio of alkyne/CuI/NBS/DIPEA was 1:0.5:1:0.5.

^b Determined by GC analysis.

In conclusion, we have successfully developed an efficient and mild method for preparation of 1,3-diynes under CuI/NBS/DIPEA promoting system. The novel copper-mediated Glaser-type coupling reaction could be completed under ambient temperature without exclusion of air and moisture. A variety of terminal alkynes including aliphatic, aromatic, and acyl acetylenes success-

fully underwent the coupling reaction to produce corresponding 1,3-diynes in high to excellent yields. Alkynes with various protective groups, and even in sugar and amino acid-building blocks could react smoothly to give the functionalized 1,3-diynes in good yield within 4 h under CuI/NBS/DIPEA promoting system. The plausible mechanisms of this novel copper-mediated coupling reaction



Scheme 2. Two plausible mechanisms for the CuI/NBS/DIPEA-mediated Glaser coupling reaction.

were discussed, and the further application of the CuI/NBS/DIPEA-mediated Glaser coupling reaction in the construction of designed sugars and peptide biomolecules is underway in our laboratory.

Acknowledgments

This work was supported by the National Natural Sciences Foundation of China (20672031, 20802017, and 20872029), the program for Innovative Research Team (in Science and Technology) in University of Henan Province (2008IRTSTHN002, 2006-HACET-06), and Innovation Scientists and Technicians Troop Construction Projects of Henan Province (084100510002).

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- General procedure for compound 2a–k*: A mixture of **1** (1 mmol), CuI(0.095 g, 0.5 mmol), DIPEA (0.167 mL, 1 mmol), and NBS (0.089 g, 0.5 mmol) in CH₃CN (10 mL) was stirred under air at room temperature for the desired time until complete consumption of starting material as judged by TLC. After the conventional workup, the residue was purified by column chromatography (petroleum ether /ethyl acetate) to give products **2a–c** and **2e–k**. For **2d**, the yield was determined by GC analysis after workup. *Spectral data for all new compounds*: Compound **2f** ¹H NMR (400 MHz, CDCl₃), δ 4.14 (t, *J* = 6.0 Hz, 4H), 2.36 (t, *J* = 6.8 Hz, 4H), 2.05 (s, 6.0H), 1.85 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 171.0, 76.1, 65.1, 62.9, 27.3, 20.9, 16.0; HEMS *m/z* calculated for C₁₄H₁₈O₄Na 273.1103, found 273.1101. Compound **2i** ¹H NMR (400 Hz, CDCl₃), δ 5.87–5.77 (m, 4H), 5.30 (d, *J* = 1.2 Hz, 2H), 5.00 (s, 2H), 4.25–4.41 (m, 4H), 4.07–4.03 (m, 2H), 3.86–3.81 (m, 2H), 3.81–3.55 (m, 2H), 2.35 (t, *J* = 6.8 Hz, 4H), 2.07 (s, 6H), 2.06 (s, 6H), 1.81 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 170.8, 170.3, 129.1, 127.6, 94.5, 67.0, 65.7, 65.2, 63.0, 28.3, 21.0, 20.8, 16.1; HEMS *m/z* calculated for C₃₀H₃₈O₁₂Na 613.2201, found 613.2201. Compound **2j** ¹H NMR (400 Hz, CDCl₃), δ 6.76 (br s, 2 H), 4.26 (q, *J* = 7.2 Hz, 4 H), 4.80 (d, *J* = 5.2 Hz, 4H), 1.30 (t, *J* = 7.2 Hz, 6 H); ¹³C NMR(100 MHz, CDCl₃) δ 168.6, 150.8, 74.2, 67.9, 62.0, 41.6, 14.1; HEMS *m/z* calculated for C₁₄H₁₆N₂O₆Na 331.0906, found 331.0903. Compound **2k** ¹H NMR (400 Hz, CDCl₃), δ 7.72–7.34 (m, 6 H), 7.14–7.09 (m, 4H), 6.67 (d, *J* = 8 Hz, 2H), 4.90 (m, 2H), 3.77 (s, 6H), 3.21–3.12 (m, 4H) ¹³C NMR(100 MHz, CDCl₃) δ 170.7, 150.2, 135.0, 129.2, 128.7, 127.4, 74.3, 67.8, 53.7, 52.6, 37.5; HEMS *m/z* calculated for C₂₆H₂₄N₂O₆Na 483.1532, found 483.1527.
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