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First synthesis of both 1-aryl-4-[(*E*)-alk-1-enyl]-1*H*-1,2,3-triazoles and 1-aryl-4-[(*Z*)-1-(trimethylsilyl)alk-1-enyl]-1*H*-1,2,3-triazoles: assembly of π-extended 1,2,3-triazoles using a cross-coupling/click reaction sequence

Asuka Oikawa, Gan Kindaichi, Yasutaka Shimotori, Masayuki Hoshi *

Department of Biotechnology and Environmental Chemistry, Kitami Institute of Technology, 165 Koen-cho, Kitami, Hokkaido 090-8507, Japan

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ABSTRACT

A practical and general synthetic approach to a series of π-extended 1,2,3-triazoles with both aryl and alkenyl moieties on the triazole ring is described. Synthesis of 1-aryl-4-[(*E*)-alk-1-enyl]-1*H*-1,2,3-triazoles can be achieved by the click reaction between terminal conjugated (*E*)-enynes, prepared by copper-mediated cross-coupling reaction of (*E*)-alk-1-enyldisiamylboranes with (trimethylsilyl)ethynyl bromide, and aryl azides, prepared from arylboronic acids and sodium azide in another flask and employed for the following click reaction without any purification. 1-Aryl-4-[(*Z*)-1-(trimethylsilyl)alk-1-enyl]-1*H*-1,2,3-triazoles can be also synthesized by a sequential three-step reaction, which involves copper-mediated cross-coupling reaction of (*Z*)-1-(trimethylsilyl)alk-1-enyldicyclohexylboranes with (trimethylsilyl)ethynyl bromide to form (*Z*)-1,3-bis(trimethylsilyl)alk-3-en-1-ynes, deprotection of the trimethylsilyl group on the alkynyl carbon atom to generate (*Z*)-3-(trimethylsilyl)alk-3-en-1-ynes and click reaction with aryl azides prepared in the same manner as described above. Both synthetic routes are tolerant of a wide range of functional groups with moderate to good yields.

1. Introduction

Since Sharpless and Meldal independently pioneered the copper(I)-catalyzed 1,3-dipolar cycloaddition reaction between organic azides and terminal alkynes to give 1,4-disubstituted 1,2,3-triazoles exclusively,[1] a wide variety of strategies have been developed for the cycloaddition reaction, the so-called click reaction.[2] As well as showing biological activities,[3] compounds bearing 1,2,3-triazole moiety have found a large number of applications in different fields such as bioconjugation[4] and materials science.[5] The 1,2,3-triazole scaffold is stable not only under acidic and basic conditions but also under oxidative and reductive conditions. The chemically robust properties can be attributed to the heterocyclic aromatic system. Assembling further π-extended 1,2,3-triazoles can be performed by introduction of substituents such as aryl and alkenyl groups into 1-, 4-, and 5-positions of the triazole ring. The extension of conjugated system on 1,2,3-triazole ring, in fact, has been realized in the click reaction by making a choice from the substrates. Thus, use of arylethynes as terminal alkynes gives 4- or 5-aryl 1,2,3-triazoles upon choosing the reaction conditions[2,6] and use of aryl and alkenyl azides furnishes 1-aryl[7–9] and 1-alkenyl[7a,h,8a,10] 1,2,3-triazoles, respectively. Although there are several reports on the formation of 4- or 5-alkenyl 1,2,3-triazoles,[6a,h,7a,c,11] the precursor of the alkenyl group is limited to only a few conjugated enynes such as 1-ethynylcyclohexene. The click reaction using terminal conjugated (*E*)-enynes (**2**), to our knowledge, is the only our previous report,[12] in which the reaction with in situ generated various benzyl azides proceeded at room temperature to afford a wide range of 1-arylmethyl-4-[(*E*)-alk-1-enyl]-1*H*-1,2,3-triazoles in high yields. As our continued interest in assembling π-extended compounds utilizing in situ generated terminal conjugated enynes,[13] we focused our attention on the copper(I)-catalyzed click reaction with aryl azides to extend π-conjugation at the 1-position as well as at the 4-position of 1,2,3-triazole. Herein, we report the first synthesis of both 1-aryl-4-[(*E*)-alk-1-enyl]-1*H*-1,2,3-triazoles (**3**) through a sequential two-step reaction and 1-aryl-4-[(*Z*)-1-(trimethylsilyl)alk-1-enyl]-1*H*-1,2,3-triazoles (**6**) through a sequential three-step reaction. The present protocol provides a practical and general way to access π-extended 1,2,3-triazoles **3** and **6**, respectively, and is applicable to a wide range of starting materials.

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* Corresponding author. Fax: +81 (157)247719; e-mail address: hoshi-m@chem.kitami-it.ac.jp (M. Hoshi).

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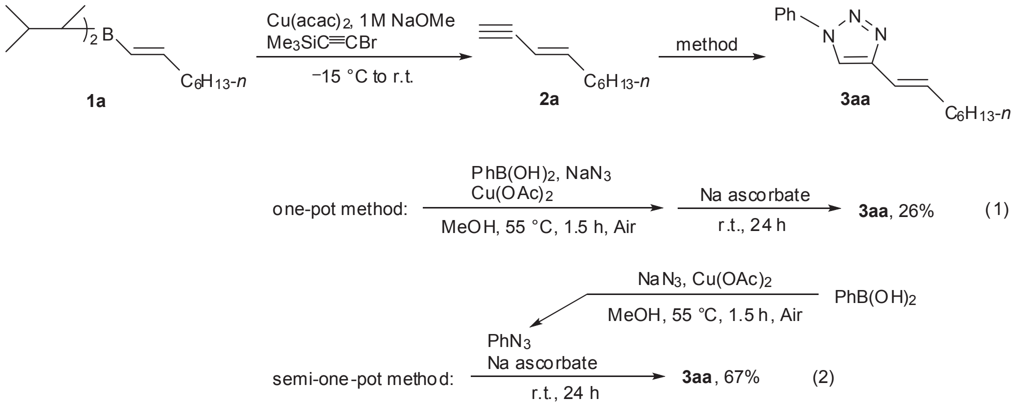
2. Results and discussion

At first, our attention was turned to one-pot synthesis of 1-aryl-4-[(*E*)-alk-1-enyl]-1*H*-1,2,3-triazoles (**3**) through a sequence of copper-mediated cross-coupling reaction of (*E*)-alk-1-enyldisiamylborane (**1**) with (trimethylsilyl)ethynyl bromide followed by click reaction with in situ generated aryl azides. Although a lot of methods have been reported for the synthesis of 1-aryl 1,2,3-triazoles employing in situ generation of aryl azides,[7–9] most of these methods suffer from limitations such as prolonged heating, use of expensive ligand, substrate or solvent, use of modified copper catalyst or unstable substrate, troublesome preparation of substrate, and low yield. Accordingly, we chose a method where the preparation of aryl azides could be performed by the reaction of sodium azide with arylboronic acids, which are stable under air and commercially readily available, in the presence of a small amount of Cu(OAc)$_2$ in methanol under an air atmosphere at 55 °C for 1–3 h.[8b] Thus, the cross-coupling reaction of (*E*)-oct-1-enyldisiamylborane (**1a**) (1.0 mmol) with (trimethylsilyl)ethynyl bromide (0.67 mmol) was carried out in the presence of Cu(acac)$_2$ (0.05 mmol) and NaOMe (1M, 0.75 mmol) at temperatures gradually rising from −15 °C to room temperature overnight to form (*E*)-dec-3-en-1-yne (**2a**). To the resulting solution of **2a**, phenylboronic acid (1 mmol), NaN$_3$ (1.5 mmol), Cu(OAc)$_2$ (0.1 mmol), and MeOH (5 mL) were added, and the reaction mixture was stirred at 55 °C in open air for 1.5 h in order to generate phenyl azide. After cooled to ambient temperature, sodium ascorbate (0.1 mmol) for reduction of Cu(OAc)$_2$ was added to the resultant mixture, which was stirred at room temperature for 24 h (Scheme 1, Eq. 1). The desired product, 1-phenyl-4-[(*E*)-oct-1-enyl]-1*H*-1,2,3-triazole (**3a**), was isolated in 26% yield based on (trimethylsilyl)ethynyl bromide, indicating that the yield of the click reaction between **2a** and phenyl azide was estimated to be less than 40%.[14] It has been recognized that the click chemistry using copper(I)-catalyzed azide-alkyne cycloaddition furnishes 1,4-disubstituted 1,2,3-triazoles in very high yields.[2] We surmised that incomplete formation of phenyl azide may be responsible for the low yield of **3a**. This guess led us to prepare phenyl azide in another flask from phenylboronic acid in the same manner as described above. After phenyl azide, thus prepared, was transferred to the flask containing **2a**, sodium ascorbate (0.1 mmol) was added to the mixture, which was stirred at room temperature for 24 h (Scheme 1, Eq. 2). To our delight, the click reaction could be improved to afford **3a** in 67% overall yield, indicating that the yield of the click reaction between **2a** and phenyl azide increased up to 90%. This result ensured sufficient potential of our protocol. While all the steps could not be carried out in a one-pot manner, each step could be performed without operation such as exchange of solvent and filtration.

Having identified the separate preparation of aryl azides from arylboronic acids as the key step, we then explored the substrate scope of this semi-one-pot transformation using various combinations of terminal conjugated (*E*)-enynes (**2**) and aryl azides. The results are shown in Table 1. The semi-one-pot process mostly afforded products **3** in moderate to good yields with excellent regio- and stereoselectivities. It should be noted that aryl azides, prepared in another flask, could be directly used for the following click reaction without any purification. Different compounds **2** were suitable in this transformation. In particular, pre-chlorinated (*E*)-enyne, (*E*)-7-chlorohept-3-en-1-yne (**2b**), was tolerated well (entries 15–21). A variety of aryl azides, bearing electron-donating groups such as methoxy (entries 2, 10 and 16) and methyl (entries 3, 11, 12 and 17), and electron-withdrawing groups such as fluoro (entries 5 and 18), acetyl (entries 6 and 19), cyano (entries 7 and 20) and nitro (entries 8, 14 and 21), worked well under the same reaction conditions. The electronic effect on the phenyl ring had little influence on the reactivity of aryl azide substrates. Unfortunately, a combination of substrates resulted in a complex mixture which could not be separated (entries 4 and 13).

We next focused on broadening the scope of enynes for the π-conjugated 1,2,3-triazole synthesis. In our previous report on the synthesis of conjugated enynes,[15] it was demonstrated that not only terminal conjugated (*E*)-enynes (**2**) but also trimethylsilyl-protected terminal conjugated enynes, (*Z*)-1,3-bis(trimethylsilyl)alk-3-en-1-ynes (**5**), could be prepared by copper-mediated cross-coupling reaction with (trimethylsilyl)ethynyl bromide under extremely mild conditions. Provided deprotection of the trimethylsilyl group attached to the alkyne moiety of **5** is performed, the deprotected compounds, (*Z*)-3-(trimethylsilyl)alk-3-en-1-ynes, can participate in click reaction. It has been reported that click reaction involving a deprotection step can be also carried out in a one-pot fashion,[16] where tetrabutylammonium fluoride (TBAF) was frequently employed as the desilylating reagent. Alternatively, it was found that a solution of NaOMe in MeOH was an efficient reagent for the deprotection of the trimethylsilyl group from **5**.[15] Our previous results as well as literature reports prompted us to examine a two-step process involving the deprotection of **5** followed by click reaction with aryl azide. Thus, the cross-coupling reaction of (*Z*)-1-(trimethylsilyl)hex-1-enyldicyclhexylborane (**4a**) (1.0 mmol) with (trimethylsilyl)ethynyl bromide (0.67 mmol) was performed in the presence of CuI (0.1 mmol) and NaOH (1M, 0.75 mmol) at temperatures gradually rising from −15 °C to room temperature overnight to form (*Z*)-1,3-bis(trimethylsilyl)oct-3-en-1-yne (**5a**). To the resulting solution of **5a**, phenyl azide, prepared from phenylboronic acid (1 mmol), NaN$_3$ (1.5 mmol), and Cu(OAc)$_2$ (0.1 mmol) in MeOH (5 mL) at 55 °C in open air for 1.5 h, was added, followed by addition of sodium ascorbate (0.1 mmol) and NaOMe (1 M, 1 mmol). The



Scheme 1. Choice of the step for the preparation of phenyl azide.