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One-pot synthesis of 1-arylmethyl-4-[(*E*)-alk-1-enyl]-1*H*-1,2,3-triazoles *via* a cross-coupling/click reaction sequence†

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1-Arylmethyl-4-[(*E*)-alk-1-enyl]-1*H*-1,2,3-triazoles have been synthesized from terminal conjugated (*E*)-enynes, prepared by copper-mediated cross-coupling reaction of (*E*)-alk-1-enyldisiamylboranes with (trimethylsilyl)ethynyl bromide, benzyl bromides and sodium azide in a one-pot fashion. In this cross-coupling/click reaction sequence, the copper precursor $Cu(acac)_2$ can serve as a tandem catalyst.

Since the discovery of the copper(I)-catalyzed 1,3-dipolar cycloaddition reaction between organic azides and terminal alkynes,[1] the cycloaddition reaction has been extensively studied by many research groups to grow the archetypal click reaction.[2] The reliable protocols have enabled the efficient and regioselective preparation of 1,4-disubstituted 1,2,3-triazoles and found a large number of applications not only to synthetic organic chemistry[2] but also to other areas such as bioconjugation[3,4] and materials science.[5,6] Most of the copper(I)-catalyzed 1,3-dipolar cycloaddition reactions with organic azides have been designed to avoid the isolation of unstable azide intermediate.[7,8] Multicomponent or one-pot click reactions in which organic azides are generated *in situ* from the corresponding organic halides[9] or organic compounds with other functionalities[10–14] and sodium azide in the presence of terminal alkynes give access to diversely substituted 1,2,3-triazoles. The diversity of alkyne is also important to gain a wide variety of substituted 1,2,3-triazoles. Although terminal conjugated enynes such as 1-ethynylcyclohexene have been used as the alkyne,[15] as far as we know, there are no reports on the synthesis of 1,2,3-triazoles using terminal conjugated (*E*)-enynes **2**. Herein, we would like to communicate our results regarding the first synthesis of 1-arylmethyl-4-[(*E*)-alk-1-enyl]-1*H*-1,2,3-triazoles **3** *via* a cross-coupling/click reaction sequence in a one-pot manner from (*E*)-alk-1-enyldisiamylboranes **1** as illustrated in Scheme 1.

In the context of our continuing interest in assembling π-extended conjugation[16] utilizing terminal conjugated enynes prepared by the copper-mediated cross-coupling reaction of alkenyldisiamylboranes with (trimethylsilyl)ethynyl bromide,[17] we envisioned that 1,3-dipolar cycloaddition reaction of compound **2** with organic azide would result in the formation of 1,2,3-triazole bearing an (*E*)-alk-1-enyl moiety. Our initial efforts focused on the reaction using benzyl bromide, sodium azide and (*E*)-dec-3-en-1-yne **2a**. Thus, the cross-coupling reaction of (*E*)-oct-1-enyldisiamylborane **1a** (1 mmol) with (trimethylsilyl)ethynyl bromide (0.67 mmol) was carried out in the presence of $Cu(acac)_2$ (0.05 mmol) and 1 M NaOMe (0.75 mmol, MeOH) at −15 °C to room temperature overnight to form compound **2a** (*ca.* 0.5 mmol).[18] After removal of solvents (THF and MeOH) under reduced pressure, **2a** was subjected to the copper(I)-catalyzed 1,3-dipolar cycloaddition reaction with benzyl azide generated *in situ* from benzyl bromide (0.5 mmol) and sodium azide (0.5 mmol) at room temperature in a mixture of different solvents. In the presence of CuI (0.2 mmol) and Et_3N (0.5 mmol) as a combination of copper source and base, the reaction was performed in a mixture of *t*-BuOH and water (1 : 1, v/v), a frequently used solvent system,[1b,2] to give the desired product, 1-benzyl-4-[(*E*)-oct-1-enyl]-1*H*-1,2,3-triazole **3aa**, in 73% yield after 24 h (Table 1, entry 1). Alternatively, using a mixture of acetone and water (2 : 1, v/v) as the solvent system, the reaction was completed in 2 h to provide a 92% yield of **3aa** (Table 1, entry 2). It was observed that the colour of $Cu(acac)_2$ changed from blue to reddish-yellow through green during the cross-coupling reaction. This observation implied formation of Cu(I) species and led us to examine the reaction in the absence of CuI. Thus the reaction proceeded without using CuI and Et_3N to afford product **3aa** in 94% (acetone-water) and 86% (*t*-BuOH-water) yields, respectively, after 24 h (Table 1, entries 3 and 4). It should be noted that the copper precursor $Cu(acac)_2$ can serve

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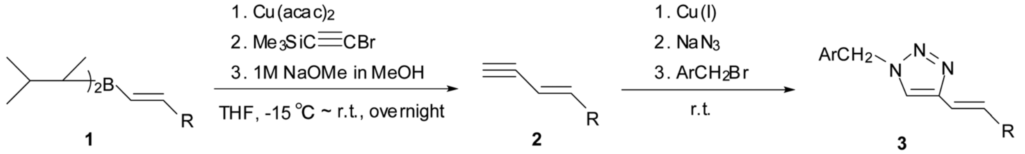
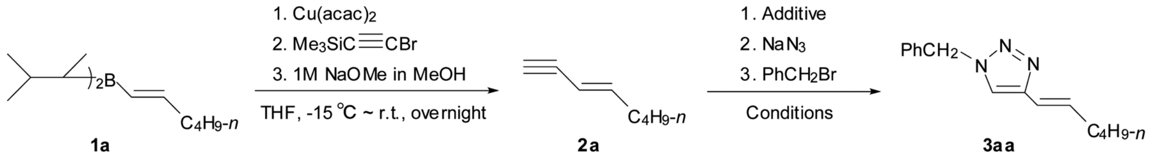


Scheme 1 The proposed one-pot synthesis of 1-arylmethyl-4-[(*E*)-alk-1-enyl]-1*H*-1,2,3-triazoles.

Table 1 Optimization of the conditions for the cycloaddition between (*E*)-dec-3-en-1-yne and *in situ* generated benzyl azide in the sequential reaction



Entry	Additive	Solvent	Time (h)	Yield of **3aa** (%)[a]
1	CuI/Et$_3$N	*t*-BuOH–H$_2$O (1 : 1)	24	73
2	CuI/Et$_3$N	CH$_3$COCH$_3$–H$_2$O (2 : 1)	2	92
3	—	CH$_3$COCH$_3$–H$_2$O (2 : 1)	24	94
4	—	*t*-BuOH–H$_2$O (1 : 1)	24	86
5	Na ascorbate	CH$_3$COCH$_3$–H$_2$O (2 : 1)	24	98

[a] Isolated yields after column chromatography (silica gel: hexane-ethyl acetate).

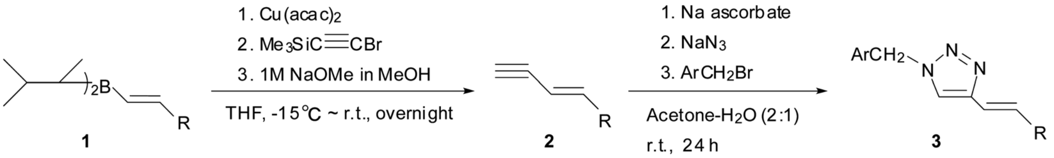
as a tandem catalyst. Using sodium ascorbate (0.1 mmol) as a reducing agent for conversion of Cu(II) to Cu(I),[1b,2] product **3aa** was obtained in 98% yield after 24 h (Table 1, entry 5). From the viewpoints of catalyst loading and product yield, using a mixture of acetone and water (2 : 1, v/v) as solvent and sodium ascorbate as reductant appeared to be the most promising reaction conditions for the click reaction step, albeit demanding longer reaction times.

We examined the scope of this one-pot reaction using compounds **1** with a structurally and electronically diverse substituent (R) and various benzyl bromides. As can be seen from Table 2, the one-pot process allowed us to obtain products **3** in good to high yields. Different types of compounds **2** derived from compounds **1** underwent smoothly 1,3-dipolar cycloaddition with *in situ* generated benzyl azide (Table 2, entries 1–4).[19] A variety of functionalized benzyl azides, generated *in situ* from commercially available functionalized benzyl bromides, could be converted into the desired products **3** (Table 2, entries 5–25). Thus, none of the functional group on the phenyl ring affected the nucleophilic substitution with sodium azide, followed by 1,3-dipolar cycloaddition even under our reaction conditions. It is noteworthy that base-labile functionalities (–CN, –CO$_2$CH$_3$) were tolerated during the course of the reaction (Table 2, entries 10, 11, 17, and 25). The substituents including chloro, bromo, cyano, and ester groups on the phenyl ring remained intact in the cycloaddition reaction, which would provide the opportunity for further chemical transformations.

Conclusions

In summary, we have realized a one-pot method for the synthesis of 1-arylmethyl-4-[(*E*)-alk-1-enyl]-1*H*-1,2,3-triazoles in good to excellent yields. This one-pot reaction includes three chemical transformations: the cross-coupling reaction between (*E*)-alk-1-enyldisiamylboranes and (trimethylsilyl)ethynyl bromide to form terminal conjugated (*E*)-enynes, the nucleophilic substitution reaction of functionalized benzyl bromides with sodium azide to generate functionalized benzyl azides, and the 1,3-dipolar cycloaddition reaction. The present protocol can, therefore, proceed without the need for isolation of both terminal conjugated (*E*)-enynes and benzyl azides. Moreover, the inherent advantage of this method is that copper species formed during the cross-coupling reaction using Cu(acac)$_2$ as catalyst can be utilized in combination with sodium ascorbate for the subsequent 1,3-dipolar cycloaddition reaction. Some features, such as tandem catalyst, mild reaction conditions, overall regio- and stereoselectivity, and good functional compatibility, make this strategy a practical and environmentally benign process for the construction of various 1-arylmethyl-4-[(*E*)-alk-1-enyl]-1*H*-1,2,3-triazoles. Studies on the elucidation of copper species derived from Cu(acac)$_2$ and the

Table 2 One-pot synthesis of 1-arylmethyl-4-[(*E*)-alk-1-enyl]-1*H*-1,2,3-triazoles through sequential copper-catalyzed reactions



Entry	R	Ar	Product	Yield (%)[a]
1	n-C_6H_{13}	Ph	**3aa**	98
2	Ph	Ph	**3ba**	92
3	$Cl(CH_2)_3$	Ph	**3ca**	89
4	Cyclohex-1-enyl	Ph	**3da**	90
5	n-C_6H_{13}	2-MeC_6H_4	**3ab**	96
6	n-C_6H_{13}	4-MeC_6H_4	**3ac**	88
7	n-C_6H_{13}	4-$CF_3C_6H_4$	**3ad**	91
8	n-C_6H_{13}	4-ClC_6H_4	**3ae**	81
9	n-C_6H_{13}	4-BrC_6H_4	**3af**	86
10	n-C_6H_{13}	4-NCC_6H_4	**3ag**	88
11	n-C_6H_{13}	4-$MeOCOC_6H_4$	**3ah**	85
12	Ph	2-MeC_6H_4	**3bb**	92
13	Ph	4-MeC_6H_4	**3bc**	80
14	Ph	4-$CF_3C_6H_4$	**3bd**	88
15	Ph	4-ClC_6H_4	**3be**	81
16	Ph	4-BrC_6H_4	**3bf**	86
17	Ph	4-NCC_6H_4	**3bg**	83
18	$Cl(CH_2)_3$	2-MeC_6H_4	**3cb**	90
19	$Cl(CH_2)_3$	4-MeC_6H	**3cc**	83
20	$Cl(CH_2)_3$	4-ClC_6H_4	**3ce**	82
21	$Cl(CH_2)_3$	4-BrC_6H_4	**3cf**	91
22	Cyclohex-1-enyl	4-MeC_6H	**3dc**	80
23	Cyclohex-1-enyl	4-$CF_3C_6H_4$	**3dd**	85
24	Cyclohex-1-enyl	4-BrC_6H_4	**3df**	80
25	Cyclohex-1-enyl	4-$MeOCOC_6H_4$	**3dh**	86

[a] Isolated yields after column chromatography (silica gel: hexane-ethyl acetate).

synthetic application of this reaction are currently under investigation in our laboratory.

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