



Phenoxide-mediated Sonogashira coupling of trimethylsilylalkynes and aryliodides: practical synthesis of phenolic-hydroxy-substituted diarylethyne and 1,4-diarylbutadiynes

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ABSTRACT

We successfully synthesized phenolic-hydroxy-substituted diarylethyne and 1,4-diarylbutadiyne from trimethylsilylalkynes and aryliodides via silyl-group-migration-induced deprotection of alkynes and the usual Sonogashira coupling. The phenol moiety, which works as a desilylating agent, can be attached to any position in the coupling partner. This improvement for Sonogashira coupling would be highly effective, especially when the coupling partner has a phenol moiety. Additionally, the stability of the migrated silyl moiety on the ethynylation of 2-iodophenol is discussed.

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Sonogashira coupling¹ is a fundamental and important reaction for the synthesis of aryl acetylene derivatives, which in turn can be applied for preparing organic and polymeric materials,² and bioactive compounds.³ Among the various applications of this reaction,⁴ coupling with silylalkynes has been actively developed,^{5–8} for the main reason that isolation of the unstable terminal alkyne intermediates is not required. This reaction involves desilylation by Cl[–] ions in a polar solvent,⁵ sec-amines,^{5h,6} oxygen nucleophiles such as alkoxides, siloxides, and hydroxides,⁷ or fluoride reagents,^{5b,8} followed by the usual Sonogashira coupling.

Phenolic-hydroxy-substituted diarylethyne and 1,4-diarylbutadiyne have the basic structure of liquid crystals, and they are synthetic intermediates for polycyclic antibiotics and functional polymers. These phenolic compounds with an alkyne functionality are synthesized frequently via Sonogashira coupling.^{3,9} However, the hydroxy group tends to undergo undesired reactions such as O-arylation;¹⁰ in particular, the *ortho* hydroxy group undergoes intramolecular cyclization to afford benzofuran.¹¹

To solve these problems, we supposed that if the silyl group on an alkyne migrates to the phenol moiety, Sonogashira coupling can be carried out without the risk of the aforementioned undesired reactions. Recently, inspired by Mukaiyama's report,¹² we developed the monoarylation of 1,3-bis(trimethylsilyl)butadiyne via monode-

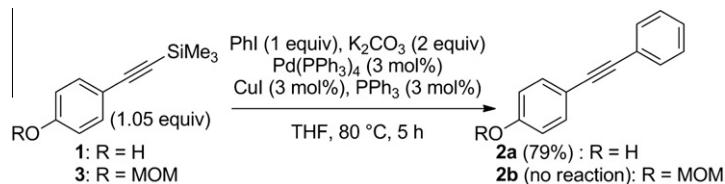
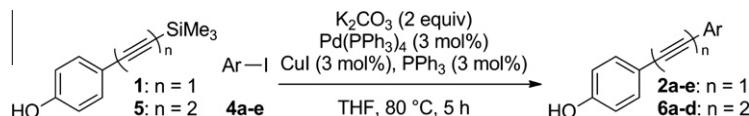
silylation by a phenoxide, on the basis of the above mentioned supposition.¹³ In this Letter, we present the efficient syntheses of hydroxyl-substituted diarylethyne and 1,4-diarylbutadiyne by silyl migration and Sonogashira coupling.

To verify the effectiveness of phenols as desilylating agents, we carried out Sonogashira coupling using 4-(trimethylsilylethynyl)phenol **1** and MOM-protected phenol **3**. Trimethylsilylethynylbenzene **1** or **3** (1.05 equiv) was treated with iodobenzene (1 equiv), Pd(PPh₃)₄ (3 mol %), Cul (3 mol %), PPh₃ (3 mol %), and K₂CO₃ (2 equiv) in THF, and the mixture was heated to 80 °C. Under these conditions, the one-pot Sonogashira coupling of **3** did not give the desired product (no conversion), but the reaction with **1** proceeded to afford the product in 79% yield (**Scheme 1**).

This protocol could also be applied to the synthesis of various diarylacetylenes, by the coupling of **1** with various aryl iodides. The results are summarized in **Table 1**. The electron-donating 4-(1-hexyloxy)iodobenzene **4b** and electron-withdrawing 4-nitro-iodobenzene **4c** underwent the coupling smoothly to afford the desired products in 82% (entry 2) and 76% yields (entry 3), respectively. However, 4-iodobromobenzene **4d** was alkynylated only at the iodide position, and the Br–C bond was not cleaved (entry 4). 3-Trimethylsilyliodobenzene **4e** was converted into diarylacetylene **2e** in 64% yield, and the desilylated product **2a** was not detected in the crude mixture by ¹H NMR (entry 5).¹⁴ The proposed protocol could be extended to diarylbutadiyne derivatives as well, under the same conditions. 4-(Trimethylsilylbutadiynyl)phenol **5** was coupled with iodobenzene **4a** to give the desired product in quantita-

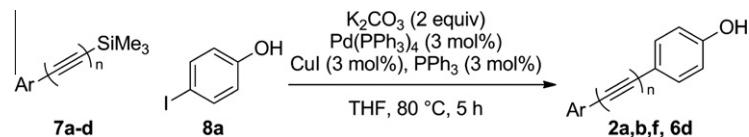
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**Scheme 1.** Sonogashira coupling with unprotected and protected trimethylsilylethynylphenol.**Table 1**
Scope of coupling 4-(trimethylsilylalkynyl)phenol **5** and various aryl iodides

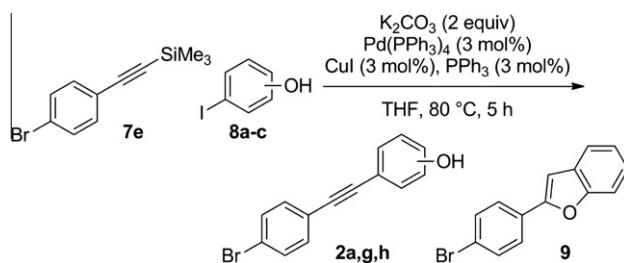
Entry	n	Ar-I	Yield (%)
1	1		79 (2a)
2	1		82 (2b)
3	1		76 (2c)
4	1		95 (2d)
5	1		64 (2e) ^a
6	2		Quant (6a)
7	2		68 (6b)
8	2		97 (6c)
9	2		64 (6d)

^a The desilylated product **2a** was not detected in the crude mixture by ¹H NMR.

Table 2
Scope of coupling 4-iodophenol with various aryltrimethylsilylalkynes

Entry	Ar-alkyne	Yield (%)
1		63 (2a)
2		81 (2b)
3		Quant (2f)
4		99 (6d)

Table 3
Scope of coupling 4-(trimethylsilylbutadiynyl) bromobenzene **7e** and iodophenols **8**



Entry	Iodophenol	Additives	Yield (%)
1	4-Iodophenol (8a)	—	72 (2a)
2	3-Iodophenol (8b)	—	85 (2g)
3	2-Iodophenol (8c)	—	72 (9)
4	8c	$\text{Cs}_2\text{CO}_3^{\text{a}}$	69 (9)
5	8c	AgOTf (2 equiv)	74 (9)
6	8c	NaH^{a}	54 (2h)
7	8c	MS4 \AA (0.9 g/mmol)	87 (2h)

^a These bases were utilized instead of K_2CO_3 .

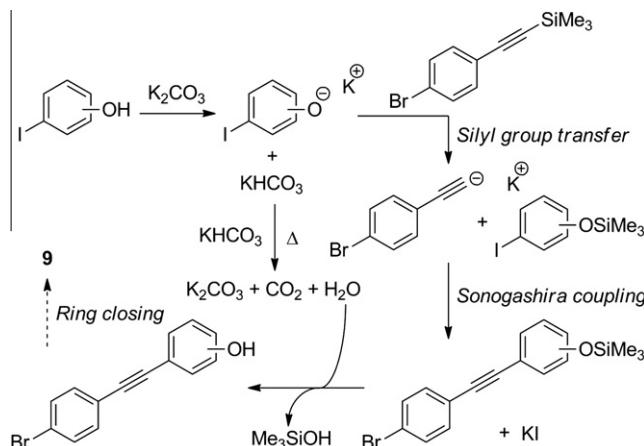


Figure 1. Plausible mechanism of removal of the trimethylsilyl group when using K_2CO_3 .

tive yield (entry 6). Other aryl iodides (**4b-d**) could also be coupled with **5** to yield the desired products in moderate-to-good yields (entries 7–9).

The aforementioned results confirmed that alkynylphenols act as a desilylating agent for trimethylsilylalkynes. Next, we investigated whether the reaction proceeds if a phenol moiety is attached to the aryl iodide and carried out the reaction of 4-iodophenol with various trimethylsilylalkynylbenzenes and trimethylsilylbutadiynylbenzene derivatives (Table 2). With trimethylsilylalkynylbenzene **7a**, the reaction proceeded at 80 °C to afford the product in 63% yield (entry 1).¹⁵ 4-(1-Hexyloxy)-1-(trimethylsilylalkynyl)benzene **7b** was also transformed into the coupling product **2b** in 81% yield (entry 2). 2-Trimethylsilylalkynylthiophene **7c**, too, afforded the coupled product **2f** in quantitative yield, although the intermediate, 2-ethynylthiophene, was highly unstable (entry 3).¹⁶ Coupling with 4-bromo-1-(trimethylsilylbutadiynyl)benzene **7d** was also successful, and the product was obtained in excellent (99%) yield (entry 4).

We next investigated the effect of the substitution position of the hydroxyl group in the iodobenzene moiety (Table 3). In this regard, we performed coupling reactions of 4-(trimethylsilylalkynyl)bromobenzene **7e** with iodophenols **8a-c** under the same conditions. While **8a, b** were smoothly transformed into the coupling products

in moderate yields (72–85%), 2-iodophenol **8c** gave benzofuran **9** in 72% yield instead of the diarylethyne **2h**. Diarylethyne **2h** could not be effectively isolated when Cs_2CO_3 was used instead of K_2CO_3 or when AgOTf was added (entries 4, 5) but was successfully isolated in 54% and 87% yields, respectively, when using NaH or adding molecular sieve 4 Å (MS4A) (entries 6, 7).

2-Alkynylphenols tend to isomerize into benzofurans via a ring-closing reaction under basic conditions and in the presence of a transition-metal catalyst.¹¹ However, in our experiments, benzofuran **9** was obtained, although the phenol moiety should have been protected by the trimethylsilyl group,^{12,13} suggesting the possible removal of the silyl group by a base. Iodide ion originated from aryl iodide acts as a base for desilylation.¹⁷ However, the results of reactions performed using Cs_2CO_3 ¹⁸ and AgOTf ¹⁹ indicated that the iodide ion did not play any role in the desilylation (Table 3, entries 4, 5). Hence, we guessed that H_2O , which is a degradate of KHCO_3 ,²⁰ worked as a desilylating agent (Fig. 1). Since both NaH and MS4 Å aided the isolation of **2h** (entries 6, 7), we concluded that the trimethylsilyl group was transferred to the phenol moiety and removed in the presence of a little water. Further, removal of the trimethylsilyl group could be prevented by adding a dehydrating agent or by using an alkali hydride instead of an alkali carbonate.

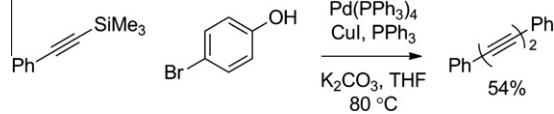
In conclusion, we successfully synthesized phenolic-hydroxy-substituted diarylethynes and 1,4-diarylbutydiynes from trimethylsilylalkynes and aryliodides via silyl-group-migration-induced deprotection of alkynes and the usual Sonogashira coupling. The phenol moiety, which works as a desilylating agent, can be attached to any position in the coupling partner. Silylation of the phenolic group helps in preventing unwanted side reactions. Various functional groups in the aryl moiety—alkoxy (electron donating), nitro (electron withdrawing), bromo, and trimethylsilyl—showed good reactivity under the reaction conditions. Removal of the migrated trimethylsilyl group could be prevented by adding a dehydrating agent or by using an alkali hydride instead of an alkali carbonate. This protocol is a strong tool for Sonogashira coupling using a phenolic-hydroxy-substituted reagent and is expected to be applicable for the synthesis of bioactive compounds and functional materials.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2013.01.091>.

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