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Silver salt-promoted direct cross-coupling reactions of alkynylsilanes with aryl iodides: synthesis of aryl-substituted alkynylamides

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Abstract

A direct cross-coupling reaction of 5-trimethylsilyl-4-pentynamides (alkynylsilanes) **1** with aryl iodides, promoted by silver carbonate in the presence of palladium catalyst, afforded aryl-substituted alkynylamides **2**, which readily underwent cyclization to form benzylidenelactams **3**. This coupling reaction proved to be a useful for synthesis of aryl-substituted alkynes. © 2000 Elsevier Science Ltd. All rights reserved.

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Palladium cross-coupling reactions between alkynylorganometallic compounds and aryl halides and related compounds are widely used in organic synthesis.¹ Many of such coupling reactions involving alkynylorganometallic compounds, such as zinc, magnesium, boron, stannane, and copper have been reported.¹ However, these alkynylorganometallic compounds are often unstable. In contrast, alkynylsilanes are versatile synthetic intermediates in organic synthesis that are stable and have been primarily used to protect terminal alkynes from organometallic reagents.² Nevertheless, there have only been a few reported examples of such direct coupling reactions of alkynylsilanes with aryl halides being carried out in the presence of F^- for activation of Si–C bonds as in Hiyama et al.³ or under basic conditions as in Rossi et al.⁴ and Huang et al.⁵ Other examples of the one-pot desilylation/coupling reaction of alkynylsilanes with acid halides by catalyzed CuCl⁶ and dimerization of alkynylsilanes by CuCl⁷ or CuOTf⁸ have been reported.

Recently, as an example of such a copper(I) salt-mediated coupling reaction, a direct Pd(0)-crosscoupling reaction of alkynylsilanes with anyl trifrates in the presence of CuCl in DMF was reported by Hiyama et al.⁹

In a previous paper, we reported that palladium cross-coupling reaction of 2-(trimethylsilylethynyl)benzamide derivatives with 3,4-(methylenedioxy)phenyl iodide in the presence of silver carbonate was a key-step in lennoxamine synthesis.¹⁰ The efficacy of this cross-coupling method

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led us to an attempt to apply it to conversion of 5-trimethylsilyl-4-pentynamides 1 (alkynylsilanes) into aryl-substituted 4-pentynamides 2, which readily underwent cyclization to form benzylidenelactams 3 (Scheme 1).¹¹



Scheme 1.

Sonogashira's procedure is the most useful method for the induction of aryl groups into a terminal alkyne.¹² However, Jacobi et al. reported that Sonogashira-type coupling reactions of 4-pentynamide derivatives with iodopyrroles (Pd(Ph₃P)₄, CuI, Et₃N in DMF) required the use of DMF as a solvent under strict anaerobic conditions in order to prevent formation of diynes arising from oxidative dimerization of 4-pentynamides.¹³

In the present paper, we focused on silver mediated direct coupling reaction of 5-trimethylsilyl-4pentynamides 4^{14} with aryl iodides under very mild conditions without fluoride ion or inorganic bases. And also, the coupling of alkyl- and phenylalkyne derivatives (5, 6 respectively), was examined. The results are summarized in Table 1.

The coupling of **4a** with 4-iodoanisole performed with 0.5 equiv. of Ag_2CO_3 (1 equiv. as Ag^+) and 5 mol% of Pd catalyst (A) in the presence of Bu_4NCl gave a coupling product **7** in 81% yield (run 1).¹⁵ In the absence of Ag_2CO_3 , no coupled product was detected under similar conditions, after isolating the starting material. In additon, the use of $K_2CO_3^5$ instead of Ag_2CO_3 was completely ineffective. Furthermore, the use of a catalytic amount of Ag_2CO_3 (0.2 equiv.) produced only a low yield. The effects of other silver salts have been examined. The use of Ag_2O^{16} instead of Ag_2CO_3 under similar conditions was also equally effective (77%), while $AgNO_3$ and AgI resulted in recovery of the starting material. The coupling with 4-chloroiodobenzene, heteroaromatic iodides such as 2-iodopyridine, 2-iodothiophen, or 3,4-(methylenedioxy)phenyl iodide successfully proceeded under similar conditions (runs 2–7). It is important to note that **4c** and **5**, which have a fluoride ion and a basic medium-sensitive functional group, respectively, showed smooth coupling with aryl iodides without any loss of the TBDMS-group. The couplings afforded their corresponding aryl-substituted alkynes in good yield (runs 8 and 9). The coupling of 1-phenyl-2-(trimethylsilyl)acetylene **6** also proceeded in a similar manner to give the corresponding diarylalkyne **14** in high yield (run 10).

In all cases, oxidative homo-coupling¹⁷ of alkynylsilanes afforded only a trace amount of corresponding symmetrical diynes, accompanied by the desired products. This may have been due to homo-coupling of **4**, **5** or **6** with whatever trace oxygen was present. In particular, with 2-iodopyridine in the presence of Pd-catalyst (A), an increase in the ratio of diyne formation was observed (run 3, product/diyne=91:9). Many palladium catalysts, such as (PPh₃)₂PdCl₂ (catalyst B) and Pd₂(dba)₃·CHCl₃ (catalyst C) were used in an attempt to minimize formation of diyne. However, none proved to be satisfactory (runs 4 and 5). In addition, the coupling of **6** with aryl bromide (4-bromoanisole) afforded only the homo-coupled product (run 11).

The reaction mechanism underlying the present coupling reaction remains to be clarified. When coupling of **4a** with 4-iodoanisole was allowed to proceed under the same conditions aside from the absence of Pd catalyst no coupled product **7** was observed, but the corresponding desilylated terminal alkyne was given in quantitative yield. Therefore, we concluded that the role of Ag_2CO_3 is a base for desilylation of trimethylsilyl group on terminal alkynes in the presence of Bu_4NCl .¹⁸ Consistent

	TMSB	Ar-I (1.3 eq.), Ag ₂ CO ₃ (0.5 eq.) Pd Catalyst (5 mol%)		Δr		- (
	4a-c, 5, 6	Bu₄NCI (1.0 eq.) THF 60°C~65°C, 2 h		7-14	+ (diyne	
Run	Alkynylsilane Pd Catalyst ^a		Aryl Iodide	Product ^b (%)	Product / Diyne ^c		
1	4a : R = ──CH ₂ ─		A	I— OMe	7 (81)	96 : 4	
2	4a		А	⊢∕_)−CI	8 (89)	97 : 3	
3	4a		А		9 (69)	91:9	
4	4a		В	I	9 (72)	90:10	
5	4a		С	N=⁄	9 (50)	76 : 24	
6	4a		А	ı√s	10 (89)	97 : 3	
7	4b : R =CH ₂ -	N H H OBn	A		11 (86)	97 : 3	
8	4c : R =CH ₂ -	O Ph N OSiMe ₂ tBu	А	IOMe	12 (82)		
9	5 : R =CH ₂	OSiMe ₂ tBu	А	IOMe	13 (84)	96:4	
10	6 : R = -		А	I	14 (92)	(2.2) ^d	
11	6		А	BrOMe	14 (0)	0 : 100	

Table 1
Direct cross-coupling reaction of alkynylsilanes with aryl iodides

^a Pd catalyst; A: Pd(OAc)₂ / PPh₃ (=1 : 4), B: (PPh₃)₂PdCl₂, C: Pd₂(dba)₃·CHCl₃ / dppe (= 1 : 2). ^b Pure products after chromatography. ^c Determined based on ¹H-NMR spectra of the crude products. ^d Isolated yield of diyne.

with this notion, previous studies have reported generation of silver acetylides through desilylation of alkynylsilanes in the presence of silver salts^{19,20} and a coupling reaction of vinyl triflates with terminal alkynes using Pd–Ag catalytic system.²¹ However, no successful isolation of silver acetylides as an intermediate in this system have been reported. Furthermore, no evidence has been obtained for the transmetallation between silver acetylides and organopalladium species.²²

The aryl coupled products 7–11 could readily be cyclized to aryl-substituted 5-methylidene-2pyrrolidinones 3 by utilizing a LiN(TMS)₂:AgOTf (=2:1) catalytic system in toluene.²³

In conclusion, a new method for direct coupling reactions of alkynylsilanes with aryl iodides to the corresponding aryl coupled product have been developed. The mild reaction conditions utilized for the present Ag_2CO_3 and Pd catalyst system should have widespread applicability for other alkynylsilanes as a general method. Work is now in progress to clarify the mechanism underlying this coupling reaction and to modify it in order to utilize a catalytic amount of Ag salt.

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- 14. Preparation of alkynylsilanes **4**: Treatment of 4-pentynamides with 2 equiv. of LDA followed by 2.5 equiv. of TMSCl afforded **4** in 93–95% yield.
- 15. Preparation of **10** (general procedure for **7–14**): To the THF suspension (2.5 ml) of **4a** (300 mg, 1.04 mmol), 2-iodothiophen (283 mg, 1.35 mmol), Ag₂CO₃ (143 mg, 0.52 mmol) and Bu₄NCl (288 mg, 1.04 mmol) was added the THF solution (1 ml) of PPh₃ (54 mg, 0.11 mmol) and Pd(OAc)₂ (12 mg, 0.028 mmol) under Ar followed by degassed procedure. The reaction mixture was heated at 60–65°C for 2 h. The resulting black suspension was quenched with ice-water and diluted with AcOEt (Et₂O for **14**) (10 ml), subsequently filtered with suction. The filtrate was extracted with AcOEt (or Et₂O), washed with sat. NaCl, dried over MgSO₄ and evaporated to give the crude product, which was purified by silica gel column chromatography (chloroform:acetone=20:1) to afford *N*-(3-methoxybenzyl)-5-(2-thienyl)-4-pentynamide **10** (277 mg, 89%). Recrystallization from *t*-BuOMe/hexane gave a colorless crystal, mp 72–73°C. ¹H NMR (300 MHz, CDCl₃) δ : 2.48 (t, *J*=7.2 Hz, 2H), 2.76 (t, *J*=7.2 Hz, 2H), 3.74 (s, 3H), 4.40 (d, *J*=5.6 Hz, 2H), 6.28 (b, 1H), 6.76–7.20 (m, 7H, Ar-H). ¹³C NMR (75 MHz, CDCl₃) δ : 16.2, 35.4, 43.7, 55.1, 74.8, 92.3, 112.9, 113.3, 119.9, 123.4, 126.3, 126.8, 129.7, 131.4, 140.0, 159.8, 170.8. EIMS *m/z* 299 (M⁺). Anal. calcd for C₁₇H₁₇NO₂S: C, 68.19, H; 5.72, N; 4.68. Found: C; 68.18, H; 5.95, N; 4.76.
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