Copper(I) Halide Catalyzed Three-Component Coupling Reaction of Aldehyde, Pyrrolidine and Stannyl- and Silylacetylene

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Abstract: An efficient three-component coupling reaction of aldehyde, pyrrolidine and tributylstannylacetylene or triphenylsily-lacety-lene to generate propargylamines has been developed by using copper(I) halides as promoters.

Key words: three-component coupling reaction, propargylamine, tributylstannylacetylene, triphenylsilylacetylene

Propargylamines are compounds that have the interesting biological properties and can provide important synthetic intermediates in natural products.¹ Multicomponent reaction is a powerful and useful synthetic tool to produce complex molecular structures from simple precursors by a one-pot procedure.² Propargylamine can be synthesized by a three-component (A³) coupling reaction of aldehyde, amine and alkyne through the activation of a terminal alkynyl C-H bond, where the acetylenic moiety is of value in organic synthesis. The three-component coupling reaction between terminal alkyne, aldehyde and secondary amine, initially restricted to arylacetylene, has been extended to some less activated alkynes by the introduction of transition metal complexes as catalysts.³ Propargylamines with terminal acetylenic functionality are important synthetic intermediates, however the reliable methods for their synthesis are relatively few. Thus, there is a need for a general yet efficient synthetic protocol to use a wide range of propargylamine derivatives. Silyl- and stannylacetylenes are alternative synthetic precursors for the purpose of three-component coupling reactions to generate the desired acetylenic propargylamines. However, tributylstannylacetylene has not been investigated due to the instability of stannyl group under the reported reaction conditions.⁴

In this report, we investigated the use of copper(I) halides as reagents for the A³-coupling reaction because they are readily available and much cheaper than gold,^{6a} silver,^{6b} ruthenium,^{6c} iridium^{3b} or other additives. Various copper(I) halides were examined for the A³-coupling reaction of benzaldehyde (1.0 equiv), pyrrolidine (1.0 equiv) and tributylstannylacetylene (1.1 equiv). The results showed that an unexpected dialkyne⁵ $\mathbf{1}$ was formed as the major product together with the destannylated propargylamine 2 (Table 1). Copper(I) species, especially CuI, showed much better catalytic property than those of copper(II) complexes. Various amount of CuI (0.1 equiv to 1.0 equiv) was introduced and investigated, and a 50 mol% of CuI to substrate was shown to give the best results. On the basis of these results, together with several literature precedents,⁶ it is believed that the A³-coupling reaction proceeded via a terminal alkyne C-H bond and activated by copper(I) species. The copper acetylide intermediate thus generated can react with the iminium ion prepared in situ from the aldehyde and pyrrolidine, to form the corresponding propargylamine. Dialkyne 1 was generated from the Hay coupling reaction² of propargylamine 2 which might be produced by the destannylation reaction of

Table 1	Optimization	of Copper	Promoter
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Bu ₃ Sn + N + H H	CuX (50 mol%) THF, r.t.		+ Ph
		1	2

		I	2	
Entry	CuX	Time	Yield (%) of 1	Yield (%) of 2
1	CuCl	41 h	7	4
2	CuBr	60 h	21	3
3	CuI	40 h	52	5
4	CuBr ₂	48 h	0	0
5	Cu(OAc) ₂	44 h	15	0

SYNLETT 2009, No. 3, pp 0441–0446 Advanced online publication: 21.01.2009 DOI: 10.1055/s-0028-1087553; Art ID: W14808ST

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Table 2 Optimization of Amine

Bu ₃ Sn + N +	H Cul (50 mol%)	$\xrightarrow{\text{Ph}}$	N + N + Ph	
		1	2	
Entry	Amine	Time	Yield (%) of 1	Yield (%) of 2
1	<i>n</i> -BuNH ₂	24 h	0	0
2	PhNH ₂	21 h	0	0
3	<i>i</i> -Pr ₂ NH	43 h	0	0
4	pyrrolidine	40 h	52	5
5	imidazole	43 h	0	0
6	Ph ₂ NH	44 h	0	0

stannyl propargylamine. Thus, a reaction mixture of compound **2**, CuI (0.5 equiv) and pyrrolidine (1.0 equiv) was further tested under the reaction conditions and dialkyne **1** (84%) was obtained (Scheme 1). It should be noted that self-coupling reaction did not occur and starting materials were recovered when pyrrolidine was absent.



Scheme 1 Self-coupling raction of Propargylamine

Different amines were investigated but pyrrolidine was the only one that could drive this coupling reaction (Table 2). No reaction occurred when primary amines, such as *n*-butylamine and aniline and secondary amines, such as diisopropylamine, diphenylamine and imidazole were introduced under the reaction conditions.

In the previous studies, 1.2–1.5 equivalents of terminal alkyne were usually used in the A³-coupling reaction. Thus, the coupling process was investigated with different molar ratios of tributylstannylacetylene to substrate. It

was interesting to observe that the destannylated propargylamine **2** was obtained as the only product when 1.5 equivalents of tributylstannylacetylene were used in this A^3 -coupling reaction (Table 3). When a higher amount of tributylstannylacetylene was introduced, no yield improvement of propargylamine **2** was resulted. With the use of the destannylated propargylamine, no other additive was needed for this A^3 -coupling reaction system, and the experimental procedure was simple to perform.

To understand the scope of this new reaction, various aldehydes were studied as the substrates (Table 4). A representative coupling procedure is given as follows: a mixture of aldehyde (1.0 mmol) and pyrrolidine (1.0 mmol) was added to a mixture of tributylstannylacetylene (1.5 mmol) and CuI (0.5 mmol) in anhydrous THF (5 mL) and the reaction mixture was stirred at room temperature. After the indicated time, water (10 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine (30 mL), dried (MgSO₄), filtered, and then the organic solvent was removed under a reduced pressure. The desired product was isolated by short-path silica gel column chromatography.

 Table 3
 Optimization of Tributylstannylacetylene Introduction Amount

Bu ₃ Sn		50 mol%) IF, r.t.	$-=-+ \bigvee_{Ph}^{N} + \bigvee_{Ph}^{N}$	*	
1	.0 equiv 1.0 equiv		1 2		
Entry	Acetylene (equiv)	Time	Yield (%) of 1	Yield (%) of 2	
1	1.1	43 h	52	5	
2	1.3	43 h	30	18	
3	1.5	40 h	0	80	
4	2.0	44 h	0	50	

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Table 4	CuI-Promoted A ³	-Coupling of	Tributylstannylacetylen	e with Aldehyde and Pyrrolidine
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Bu ₃ Sn +			Cul (50 mol%) THF, r.t.	\bigvee_{N}
1.5 equiv	1.0 equiv	1.0 equiv		R

Entry	R	Time	Yield (%)
1	Et−}-	27 h	40ª
2		23 h	98
3	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	25h	98
4	52-5- 7- 7-	24 h	91
5	F	26 h	91
6	CI	26 h	83
7	Br	24 h	90
8	MeO	25 h	88
9		23 h	48
10	Ks	22 h	64
11	N H	25 h	13
12	N Ts	27 h	58
13	1325 N	24 h	30

^a The low yield was obtained due to the high volatility of the product.

As shown in Table 4, reactions using aliphatic aldehydes (entries 1–3), electron-poor (entries 5–7) or electron-rich (entry 8) benzaldehydes, or heteroaromatic aldehydes (entries 9–13) gave the desired products in good to moderate yields. Aliphatic aldehydes having an α -hydrogen (entries 1–3) displayed high reactivity and gave clean reaction product under standard reaction conditions. Furthermore, heteroaromatic aldehyde such as pyrrole also gave the desired product (entry 11). However, protected *N*-acetylpyr-

role did not generate any desired product and starting material was recovered under the reaction conditions.

The terminal alkynyl propargylamine could be obtained from an A³-coupling reaction of tributylstannylacetylene, pyrrolidine and aldehyde. We are also interested in the formation of masked terminal alkynyl propargylamine and silylacetylene might be a good choice for the A³-coupling reaction as it allows for a subsequent cleavage to the terminal alkyne.⁷ Therefore, we further investigated this

Ph ₃ Si + N 1.1 equiv 1.0 ec	+ Cui H Cui	$\begin{array}{c} X (50 \text{ mol}\%) \\ \hline THF, r.t. \\ Ph \end{array}$	++ Ph	SiPh ₃
Entry	CuX	Time	Yield (%) of 1	Yield (%) of 3
1	CuCl	41 h	3	8
2	CuBr	25 h	0	29
3	CuI	25 h	0	10
4	Cu(OAc) ₂	44 h	4	0

Table 5 Optimization of Copper Promoter

 Table 6
 Optimization of Reaction Conditions

Ph ₃ Si	√ +	CuBr (50 mol%)	= - + + + + + + + + + + + + + + + + + +		
1.5 equiv	1.8 equiv 1.0 equiv		1 3	`SiPh ₃	
Entry	Energy source	Time	Yield (%) of 1	Yield (%) of 3	
1	r.t.	32 h	0	39	
2	MW (15 W)	90 min	0	80	
3	MW (30 W)	90 min	1	79	

A³-coupling reaction by using triphenylsilylacetylene as the masked terminal alkyne. A reaction mixture of triphenylsilylacetylene, pyrrolidine and benzaldehyde with different copper promoters was investigated and the results showed that CuBr was the best choice for the reaction (Table 5). Promoters of CuCl and Cu(OAc)₂ generated small amount of dialkyne **1** after prolong reaction time.

CuBr as a promoter produced the highest yield of silyl propargylamine at room temperature after 25 hours stirring. The formation of silyl propargylamine increased slightly when 1.5 equivalents of triphenylsilylacetylene and 1.8 equivalents of pyrrolidine were introduced at room temperature after 32 hours stirring. Recently, microwave radiation has been used to promote three-component coupling reaction of aldehyde, alkyne, and amine for the generation of propargylamine.^{6,8} Thus, we employed microwave as energy source to promote this A³-coupling re-

action. A much higher yield of silyl propargylamine (80%) was obtained when 15 watts of microwave power was used after 90 minutes irradiation (Table 6). A trace amount of dialkyne **1** was also produced when the microwave irradiation was increased to 30 watts under the reaction conditions.

Using triphenylsilylacetylene, the same series of aldehydes was also investigated for A^3 -coupling reaction under microwave irradiation (Table 7). Product yields of reactions using triphenylsilylacetylene with aliphatic aldehydes (entries 1–3), electron-poor (entries 5–7) or electron-rich (entry 8) benzaldehydes were lower than those of using tributylstannylacetylene. Heteroaromatic aldehydes (entries 9–11) also reacted with pyrrolidine and triphenylsilylacetylene to give products in higher yields than those treated with tributylstannylacetylene.

Ph ₃ Si + R'	O H H D equiv 1.8 equiv CuBr (50 m THF, 80 ° MW (15 V	DI%) C, W) SiPh ₃		
Entry	R	Time	Yield (%)	
1	Et− <u></u> }-	90 min	77	
2		90 min	60	
3	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	90 min	83	
4		90 min	80	
5	F	90 min	48 + 18 ^b	
6	CI	90 min	65	
7	Br	90 min	64	
8	Meo	90 min	65	
9	<u> </u>	90 min	53	
10		90 min	60	
11	N H	90 min	30	
12	N Ts	90 min	77	
13	5-5-7 	90 min	43	

 Table 7
 CuBr-Promoted A³-Coupling Reaction of Triphenylsilylacetylene with Aldehyde and Pyrrolidine^a

^a A reaction mixture of triphenylsilylacetylene (1.5 mmol), CuBr (0.5 mmol), aldehyde (1.0 mmol), pyrrolidine (1.8 mmol) and anhyd THF (5 mL) in a pressure tube with a threaded Teflon cap was microwave irradiated with 15 W power at 80 °C (CEM Discovery microwave reactor). ^b The yield of desilylated propargylamine.

In summary, an efficient three-component coupling reaction of aldehyde, pyrrolidine and tributylstannyl- or triphenylsilylacetylenes to generate the corresponding propargylamines has been achieved by using copper(I) halides as promoters. In addition, no other additive was needed for this A³-coupling reaction system, and the experimental process was quite simple to perform. **Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We would like to thank Taiwan's National Science Council (NSC 95-2113-M-032-003-MY3) and Tamkang University for their financial support.

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