A Highly Effective Pd/Cu-Catalyzed Coupling Reaction of Terminal Alkynes with Organic Halides Promoted by Tetrabutylammonium Fluoride or Hydroxide

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Abstract: Coupling reaction of terminal alkynes catalyzed by Pd/ Cu with several organic electrophiles is shown to proceed by use of tetrabutylammonium fluoride (TBAF) or tetrabutylammonium hydroxide (TBAOH) as an activator. Treatment of 1-octyne and 4-methoxy-iodobenzene in the presence of 2.0 equiv of TBAOH, 1 mol% of PdCl₂(PPh₃)₃, and 2 mol% of CuI affords 1-phenyl-1-octyne in 98% yield after stirring at room temperature for 1 h. The new coupling reaction is also applied to polymer synthesis via polycondensation of a diyne and a diiodoarene.

Key words: Sonogashira-Hagihara coupling, Pd/Cu catalyst, terminal alkynes, tetrabutylammonium fluoride, tetrabutylammonium hydroxide, polycondensation

Sonogashira-(Hagihara) coupling, the reaction of a terminal alkyne with various organic halides catalyzed by Pd/ Cu systems, is a powerful tool for the introduction of an alkynyl moiety into a variety of organic molecules and has been widely utilized in synthetic organic chemistry (eq 1).¹ A major procedural disadvantage of the Sonogashira coupling, however, is the requirement for large amounts of amine as solvent or co-solvent. The removal of the usually high boiling amine from the reaction mixture can be a serious procedural difficulty. If the amount of amine required could be decreased or eliminated altogether, the utility of the Sonogashira coupling would be significantly enhanced. Buchwald and Fu recently described one possible solution to this problem, by the tuning of phosphine ligand of the palladium catalyst. It was found that t-Bu₃P, a bulky and electron donating ligand could affect the Sonogashira coupling using only an equimolar amount of amine.²

An alternative solution was described in our recent study on the palladium-catalyzed coupling of a terminal alkyne that proceeds by the action of a promoter such as Ag_2O , tetrabutylammonium fluoride (TBAF) or tetrabutylammonium hydroxide (TBAOH) (eq 2).³ Under these conditions, the reaction takes place without the addition of any amine. During further study it was revealed that the addition of a catalytic amount of CuI to our reaction system improved the reaction rate dramatically. Accordingly, a reaction equivalent to the Sonogashira coupling is available using neither a stoichiometric nor excess amount of amine at room temperature when the reaction is carried out with TBAF or TBAOH as an activator.



Equation 1





The reaction of 1-octyne (1) with iodobenzene (2a) was carried out using 1 mol% of PdCl₂(PPh₃)₂, 2 mol% of CuI, and 2.0 equivalents of TBAF in THF. The reaction was complete after stirring at room temperature for 3 h. The reaction was clearly accelerated by the addition of a catalytic amount of CuI, since in its absence, there was no reaction at room temperature, although 59% yield of the desired product was obtained after 6 h at 60 °C.^{3a}

The Table summarizes the reactions of several terminal alkynes and organic halides. The use of 2.0 molar equivalents of TBAF seems to be optimum to affect the reaction within a short reaction period although reaction was observed with smaller amounts (1.2 equiv) of TBAF. The reactions with aryl iodides bearing an electron-withdrawing or -donating substituent, such as 4-methoxy-1-iodobenzene (2b) and 4-cyano-1-iodobenzene (2c), were found similarly useful affording the corresponding coupled products in 98% and 92% yields, respectively, after stirring for 6 h. Several aryl or alkenyl bromides were also reactive organic electrophiles. Tetrabutylammonium hydroxide (TBAOH) was found to be equally effective as an activator. It should be pointed out that the TBAOH employed was a 40% aqueous solution suggesting that the coupling reaction can be performed in the presence of a significant amount of water. The reactions could also be performed with alkynes bearing a hydroxy group, such as 3-butyn-1-ol (4), 3-butyn-2-ol (5), and 2-methyl-3-butyn-2-ol (6) to afford the corresponding coupling products in good yields. In addition, the coupling reaction with an alkyne bearing a primary amino group 7 proceeded although the reaction was found to be slower.

649

alkyne	halide		activator (equiv)	temp, °C	time, h	%yield
ⁿ С ₆ H ₁₃ ———Н		2a)	TBAF (2.0)	rt	3	93
1	⊢∕∕−OMe (2	2b)	TBAF (2.0)	rt	6	98
			TBAOH (1.2)	rt	6	98
			TBAOH (2.0)	rt	1	>99 ^b
	I	2c)	TBAF (1.2)	rt	6	92
	Br-COMe		TBAF (2.0)	rt	24	>99 ^{b,c}
PhH	2a		TBAF (1.2)	rt	42	93
(3)	2b		TBAF (2.0)	rt	36	99
(3)			TBAOH (2.0)	rt	5	>99
	Br-OMe		TBAOH (2.0)	rt	24	37 ^{b,d}
	2c		TBAF (1.2)	rt	24	>99
	I-COMe (2	2d)	TBAF (2.0)	rt	24	84
	Br-COMe		TBAOH (2.0)	rt	7	>99 ^{b,c}
	Br		TBAF (2.0)	rt	5	89
	MeO I (2f)		TBAOH (1.2)	60	5	95
HOCH ₂ CH ₂ ————————————————————————————————————	2b		TBAOH (2.0)	rt	3	83
Ме НО (5)	2b		TBAOH (2.0)	rt	3	89
Me Me HO (6)	2b		TBAOH (2.0)	rt	5	95
$H_{2N} \xrightarrow{Et} H_{2N} \xrightarrow{Et} H_{2N} \xrightarrow{Et} H_{2N} \xrightarrow{H} H_{2N} \xrightarrow{(7)} H_{2N$	2b		TBAOH (2.0)	rt	120	90

a) Unless noted, the reaction was carried out using 1 mol% of $PdCl_2(PPh_3)_2$ and 2 mol% of CuI in THF. b) The yield was estimated by ¹H NMR using trichloroethylene as an internal standard. c) $PdCl_2(PPh_3)_2$ (3 mol%) was used. d) $PdCl_2{P(o-tol)_3}_2$ (3 mol%) was used.

Sonogashira reactions are reported to proceed at room temperature when the reaction is carried out with excess amine,^{1,4} however, decreasing the amount of amine considerably retards the reaction. Indeed, comparison of the reaction of 1-octyne and 4-methoxy-1-iodobenzene under TBAF-promoted conditions with the reaction employing 1.5 equivalents of several amines at room temperature

showed that the TBAF-promoted reaction was far superior as shown in Scheme 1. Although the Sonogashira reaction using a substrate bearing an electron-withdrawing substituent with a smaller amount of Et_3N (1.5 equiv) has been shown to proceed under mild conditions,^{5,6} aryl halides bearing an electron-donating substituent should obviously be reacted under our TBAF-promoted conditions.



Scheme 1 Activator; TBAF (77%), Et₃N (14%), piperidine (20%), Et₃NH (33%), ¹Pr₂NH (15%)

The present coupling conditions were successfully applied to the polycondensation of a bifunctional alkyne and a dihalogenated aromatic compound.⁷ The reaction of 1,7-octadiyne with 1,4-diiodobenzene was carried out in the presence of catalytic $PdCl_2(PPh_3)_2/CuI$ and TBAOH to afford the corresponding polymer in good yield (eq 3). Such a polymerization has not been achieved at room temperature without CuI.^{3c}



Equation 3 55%, $M_{\rm n} = 7800$, $M_{\rm w}/M_{\rm n} = 3.7$

A typical experimental procedure for the reaction of 1-octyne and iodobenzene is as follows: To a solution of $PdCl_2(PPh_3)_2$ (3.5 mg, 0.005 mmol) and CuI (1.9 mg, 0.01 mmol) in 3 mL of THF was added successively iodobenzene (0.056 mL, 0.5 mmol), 1-octyne (0.089 mL, 0.6 mmol), and TBAF (1 mL, as 1 M THF solution, 1.0 mmol) under argon atmosphere. Stirring was continued at room temperature for 3 h and the resulting mixture was passed through a Celite pad. The filtrate was concentrated and subjected to column chromatography on silica gel (hexane-ethyl acetate, 50:1) to afford 87 mg of 1-phenyl-1-octyne (93%).

References and Notes

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651

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