Low Temperature Sonogashira Coupling Reaction

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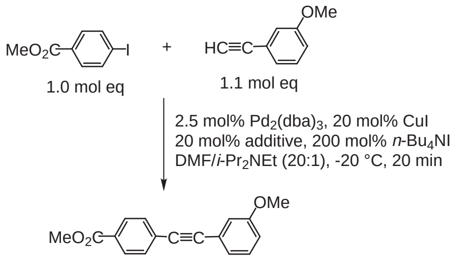
Abstract: A low temperature Sonogashira reaction was developed, which coupled equimolar amount of aryl iodide possessing electron-withdrawing groups with aromatic acetylene at -20 °C in quantitative yield.

Key words: Sonogashira coupling reaction, n-Bu$_4$NI, tris(2,4,6trimethylphenyl)phosphine, aryl iodide

Sonogashira coupling reaction is a well-established method which couples terminal acetylene and aromatic halides or triflates.[1] The reaction is catalyzed by palladium/copper complex in the presence of amine base, and is generally conducted at room temperature or higher temperature.[2,3] During our investigations on the synthesis of macrocyclic acetylenic compounds possessing helicene unit[4] we needed a rapid Sonogashira coupling reaction which can be used for the effective macrocyclization. Described here is a new protocol, which gives diarylacetylenes quantitatively at -20 °C.

Table 1. Effect of Additives on the Sonogashira Coupling Reaction.



entry	ligand	mol%	yield/%
1	none		41
2	none [a)]		0
3	PPh$_3$	20	32
4	(p-Tol)$_3$P	20	39
5	(o-Tol)$_3$P	20	52
6	(2,4,6-triMeC$_6$H$_2$)$_3$P	20	quant
7	(2,4,6-triMeC$_6$H$_2$)$_3$P	10	85
8	Ph$_3$PO	20	82
9	C$_6$H$_5$OH	20	85
10	C$_6$H$_5$OH [b)]	20	60
11	2,6-di(t-Bu)C$_6$H$_3$OH	20	70
12	2,6-di(t-Bu)C$_6$H$_3$OH [b)]	20	92
13	p-NO$_2$C$_6$H$_4$OH	20	57
14	p-MeOC$_6$H$_4$OH	20	60

a) In the absence of n-Bu$_4$NI. b) Methyl m-iodobenzoate was used.

Methyl p-iodobenzoate was treated with 1.1 mole equivalents of m-methoxyphenylacetylene in DMF/i-Pr$_2$NEt (20:1) in the presence of 2.5 mol% of Pd$_2$(dba)$_3$ (dba = dibenzylideneacetone), 30 mol% of CuI, 200 mol% of n-Bu$_4$NI, and 20 mol% of additives at -20 °C for 20 min (Table 1). While 41% yield of the coupling product was obtained under the conditions (entry 1) no reaction occurred in the absence of n-Bu$_4$NI (entry 2). Thus, the ammonium salt turned out to be essential for the low temperature coupling reaction.[3] Other iodides such as (n-C$_8$H$_{17}$)$_4$NI, Et$_4$NI, or BnEt$_3$NI were less effective. Effect of ligands which are capable to coordinate with palladium metal was then examined for the further acceleration. While triphenylphosphine was not effective (entry 3), introduction of methyl group at the *ortho*-position improved the yield (entries 4 and 5). It was finally found that the use of 20 mol% of a hindered triarylphosphine, tris(2,4,6-trimethylphenyl)phosphine, gave the product in quantitative yields in 20 min (entry 6). The yield decreased when 10 mol% of the phosphine was used (entry 7). Phosphine oxide was another good promoter (entry 8). It may be interesting to note that phenols also effectively promoted the coupling reaction (entries 9-14).[5] The substituent effect on the phenol ring appeared to be relatively unimportant. In all these reactions, purification of CuI[6] was critical to obtain reproducible results.

The coupling reaction of several aryl iodides possessing electron-withdrawing groups and arylacetylene either under the phosphine conditions (Method A) or phenol conditions (Method B) gave the corresponding diarylacetylene in quantitative yield (Table 2). The organopalladium species appeared to be more stabilized under the Method A conditions than under the Method B conditions, and formation of palladium black was suppressed in the former. In some cases, however, the coupling reaction proceeded more rapidly under the phenol conditions. The reaction completed in most cases within 60 min at -20 °C using approximately equimolar amounts of the substrates. The reaction of several reactive aryl iodides took place even at -50 °C. The catalysts load could be decreased as much as 0.1 mol%. Dimeric acetylene which was often the serious byproduct in the Sonogashira reaction was not detected under the present conditions. Biscoupling reaction of decyl 3,5-diiodobenzoate using 2.1 mol equivalents of an arylacetylene is shown in Scheme 1, which also demonstrated the effectiveness of the present coupling method. Effect of the substituents on the arylacetylene was small, and those with electron-withdrawing and electron-donating groups gave the product in high yields. In

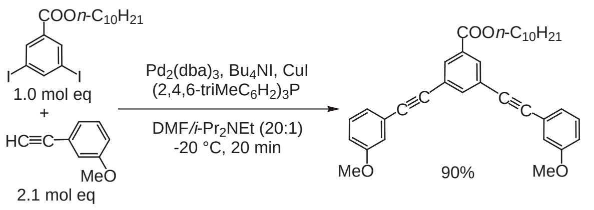
Table 2. Low Temperature Sonogashira Coupling Reaction.

$$\mathrm{ArI} + \mathrm{HC{\equiv}CAr'} \xrightarrow[\text{DMF}/i\text{-}\mathrm{Pr_2NEt}\ (20:1),\ -20\ ^\circ\mathrm{C}]{\mathrm{Pd_2(dba)_3},\mathrm{CuI},\ n\text{-}\mathrm{Bu_4NI}\ \text{ligand}} \mathrm{ArC{\equiv}CAr'}$$

Ar	Ar'	method[a]	time/min	yield/%
p-$MeO_2CC_6H_4$	Ph	A	60	98
	p-$MeOC_6H_4$	A	40	quant
	m-$MeOC_6H_4$	A	20	quant
		A [b]	240	98
		A [c]	570	88
		B	60	86
	o-$MeOC_6H_4$	A	20	quant
		A [b]	150	99
	p-MeC_6H_4	A	80	86
	m-MeC_6H_4	A	40	quant
		A [b]	300	79
	p-ClC_6H_4	A	20	93
	m-ClC_6H_4	A	20	quant
	o-ClC_6H_4	A	60	quant
p-$NO_2C_6H_4$	*m*-$MeOC_6H_4$	A	60	87
		B	60	99
		B [b]	120	74
p-$CH_3COC_6H_4$	*m*-$MeOC_6H_4$	A	60	98
	p-MeC_6H_4	A	60	93
p-$CF_3C_6H_4$	*m*-$MeOC_6H_4$	A	20	95
		B	20	92
m-$MeO_2CC_6H_4$	Ph	B	90	82
	m-$MeOC_6H_4$	A	60	97
		B	20	92
	m-MeC_6H_4	B	40	quant
	o-MeC_6H_4	B	60	92
m-$NO_2C_6H_4$	*m*-$MeOC_6H_4$	A	60	93
		B	60	quant
m-$CF_3C_6H_4$	*m*-$MeOC_6H_4$	A	20	90
		B	20	quant

a) Method A: Tris(2,4,6-trimethylphenyl)phosphine was used. Method B: 2,6-Di(*t*-butyl)phenol was used. See experimental procedures for other reaction conditions. b) Reaction was conducted at -50 °C. c) The aryl iodide (1.8 mmol) and acetylene (1.9 mmol) were reacted in the presence of $Pd_2(dba)_3$ (0.1 mol%), CuI (2.5 mol%), phosphine (1.5 mol%), and *n*-Bu_4NI (3.7 mmol) in DMF (10 mL) and *i*-Pr_2NEt (0.5 mL).

contrast, the substituent effect of the aryl halides was substantial. Reactions of aryl iodides lacking the electron withdrawing group, e.g. phenyl iodide, *p*-tolyl iodide, or *p*-methoxyphenyl iodide, stopped before completion with concomitant formation of palladium black.



Scheme 1

In summary, rapid Sonogashira coupling reaction which completed at -20 °C in less than 60 min giving quantitative yield of the coupling product was developed.

Typical procedures are as follows. Under an argon atmosphere, a mixture of methyl *p*-iodobenzoate (99 mg, 0.38 mmol), cuprous iodide (22 mg, 0.11 mmol), *n*-Bu_4NI (280 mg, 0.76 mmol), and tris(2,4,6-trimethylphenyl)phosphine (29 mg, 0.076 mmol) in DMF (4 mL) and *i*-Pr_2NEt (0.2 mL) was freeze-evacuated three times. Then, $Pd_2(dba)_3 \cdot CHCl_3$ (9.8 mg, 0.009 mmol) was added, and the mixture was stirred at room temperature for 5 min. After cooled to -20 °C, *m*-methoxyphenylacetylene (50 mg, 0.38 mmol) was added, and stirring was continued for another 20 min at the temperature. Then, the reaction was quenched by adding saturated aqueous NH_4Cl, and the organic materials were extracted twice with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The product (101 mg, quant.) was obtained by silica gel chromatography (hexane : ethyl acetate = 10:1).

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